Antiemetic/Antivertigo Agents
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Antiemetic Drugs	Manufacturer	Indication(s)
NK_1 receptor antagonist		
aprepitant (Emend®)[1]	Merck	In combination with other antiemetic agents for: ▪ Prevention of acute and delayed nausea and vomiting (N/V) associated with highly emetogenic cancer chemotherapy (initial and repeat dosing), including high-dose cisplatin in patients ≥ 12 years old and those < 12 years who weigh at least 30 kg ▪ Prevention of N/V associated with initial and repeat courses of moderately emetogenic cancer chemotherapy in patients ≥ 12 years old and those < 12 years who weigh at least 30 kg ▪ Prevention of post-operative N/V in adults
fosaprepitant dimeglumine (Emend® for injection)[2]	Merck	In combination with other antiemetic agents for: ▪ Prevention of acute and delayed N/V associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin ▪ Prevention of N/V associated with initial and repeat courses of moderately emetogenic cancer chemotherapy
rolapitant (Varubi™)[3]	Tesaro	In combination with other antiemetic agents for: ▪ Prevention of acute and delayed N/V associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy
$5\text{-}HT_3$ antagonists		
dolasetron (Anzemet®)[4,5]	Sanofi-Aventis	Oral tablets: ▪ Prevention of N/V associated with moderately emetogenic cancer chemotherapy; including initial and repeat courses in adults and children two years of age and older ▪ Prevention of post-operative N/V in adults and children two years of age and older Injection: Prevention/treatment of post-operative N/V
granisetron [6,7]	generic	▪ Prevention of N/V associated with initial and repeat courses of emetogenic cancer therapy including high-dose cisplatin ▪ Prevention of N/V associated with radiation, including total body irradiation and fractionated abdominal radiation Injection: Prevention and treatment of post-operative N/V in adults
granisetron transdermal (Sancuso®)[8]	ProStrakan	Prevention of N/V in patients receiving moderately or highly emetogenic chemotherapy regimens of up to five consecutive days duration
ondansetron (Zofran®, Zuplenz®)[9,10,11]	generic, GlaxoSmithKline, Par	Oral and Injectable (Zofran): ▪ Prevention of N/V associated with initial and repeat courses of moderately emetogenic cancer chemotherapy ▪ Prevention of post-operative N/V Oral (Zuplenz): ▪ Prevention of N/V associated with highly emetogenic cancer chemotherapy, including cisplatin ≥ 50 mg/m^2 ▪ Prevention of N/V associated with radiotherapy in patients receiving total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen

FDA-Approved Indications (continued)

Antiemetic Drugs	Manufacturer	Indication(s)
5-HT$_3$ antagonists (continued)		
palonosetron (Aloxi®)[12]	Eisai	▪ Prevention of acute and delayed N/V associated with initial and repeat courses of moderately emetogenic cancer chemotherapy ▪ Prevention of acute N/V associated with initial and repeat courses of highly emetogenic cancer chemotherapy ▪ Prevention of post-operative N/V for up to 24 hours following surgery
Combination products		
netupitant/palonosetron (Akynzeo®)[13]	Eisai	Prevention of acute and delayed N/V associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy.
Cannabinoids		
dronabinol (Marinol®)[14]	generic, Abbott	▪ Treatment of N/V associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments ▪ Anorexia associated with weight loss in patients with AIDS
nabilone (Cesamet®)[15]	Meda	Treatment of N/V associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments
Antidopaminergic Agents		
metoclopramide (Metozolv® ODT)[16]	generic, Salix	▪ Relief of heartburn symptoms of refractory gastroesophageal reflux disease (GERD) when other treatments do not work ▪ Relief of symptoms of slow stomach emptying in patients with diabetes (diabetic gastroparesis)
metoclopramide (Reglan®)[17,18,19]	generic, Ani	▪ Relief of symptoms associated with acute and recurrent diabetic gastroparesis ▪ Prevention of N/V associated with emetogenic cancer chemotherapy ▪ Prevention of post-operative N/V ▪ Small bowel intubation ▪ As short-term therapy for adults with symptomatic, documented gastroesophageal reflux (GERD)who fail to respond to conventional therapy
Antihistamines		
doxylamine/pyridoxine (Diclegis®)[20]	Duchesnay	Treatment of N/V of pregnancy in women who do not respond to conservative management
Others		
phosphorated carbohydrate solution (Emetrol® OTC)[21,22]	WellSpring	Relief of nausea due to upset stomach from intestinal flu, stomach flu, and food or drink indiscretions
trimethobenzamide (Tigan®)[23,24]	generic, JHP	Treatment of N/V associated with gastroenteritis

FDA-Approved Indications (continued)

Antivertigo Drugs	Manufacturer	Indication(s)
Antihistamines[25,26]		
dimenhydrinate (Dramamine® OTC)	generic, McNeil	▪ Treatment and prevention of motion sickness ▪ Treatment of N/V
diphenhydramine (Benadryl®)	generic, McNeil	Treatment and prevention of N/V associated with motion sickness
meclizine (Antivert®, Bonine®)	generic, Pfizer, Insight, McNeil	Treatment and prevention of N/V associated with motion sickness
Phenothiazines[27,28]		
prochlorperazine (Compro®)	generic, Paddock Labs	▪ Control of severe N/V ▪ Preoperative nausea control ▪ Treatment of N/V
promethazine (Phenergan®)	generic, West-Ward	▪ Treatment and prevention of N/V associated with motion sickness ▪ Prevention and control of N/V associated with certain types of anesthesia and surgery
Anticholinergics		
scopolamine (Transderm-Scop®)[29]	generic, Novartis	▪ Treatment and prevention of motion sickness ▪ Prevention of post-operative N/V ▪ Treatment of N/V

Cyclizine is no longer available.

OVERVIEW

Chemotherapy-induced vomiting (emesis) and nausea can significantly impact a patient's quality of life, leading to poor compliance with future chemotherapy or radiation treatments. In addition, nausea and vomiting can lead to several adverse events, such as nutrient depletion, metabolic imbalances, erosion of self-care, anorexia, diminished performance and mental status, wound dehiscence, tears in the esophagus, and cessation of potentially useful or curative cancer treatment. Approximately 70% to 80% of all cancer patients receiving chemotherapy experience nausea and/or vomiting, whereas 10% to 44% experience anticipatory nausea and/or vomiting. Furthermore, more than 90% of patients using highly emetogenic chemotherapeutic agents will experience acute emesis; however, only approximately 30% of these patients will experience a vomiting episode if they receive an antiemetic prior to their highly emetogenic chemotherapeutic treatment.[30]

There are several different factors that influence the incidence and severity of nausea and vomiting due to chemotherapy or radiation, including the specific chemotherapy medication(s) used, emetogenic potential of the chemotherapy agent(s), dose of chemotherapy agent(s), chemotherapy regimen and route of administration, amount and location of radiation therapy, and the individual patient response.[31,32]

The goal of antiemetic therapy is to prevent nausea and vomiting (N/V) completely.[33,34] As a result of research over the last 20 years, this goal is achieved for many patients receiving chemotherapy or radiation therapy. Research has increased understanding of the pathophysiology of these symptoms and has resulted in therapy that is more effective and safer than in the past. With currently available agents, complete control of emesis (e.g., no vomiting) is achievable in the majority of patients in the

first 24 hours and in approximately 45% of patients during the first week of chemotherapy. Even though vomiting can often be prevented or reduced significantly using prophylactic antiemetic medications, nausea is often times much harder to control. Complete control correlates highly with patient perception of emesis and with patient satisfaction with their emetic control.

Nausea, the perception that emesis may occur, can be judged only by the patient. Nausea is quantified by the use of various questionnaires, such as visual analog scales (VAS).[35,36,37] The incidence of nausea correlates well with the incidence of vomiting, although chemotherapy-induced nausea occurs at a greater frequency.[38,39] Total control (no nausea or vomiting) is ideal, but lesser control rates, such as major control (fewer than 3 emetic episodes) or minor control (3 to 5 emetic episodes), may still have some value in difficult emetic situations. The prevention of delayed emesis and anticipatory emesis is equal in importance to the need to prevent acute (within first 24 hours) chemotherapy- and radiation-induced emesis.[40,41]

The 2011 American Society of Clinical Oncology (ASCO) antiemetic guidelines recommend the choice of antiemetic treatment should be based on the chemotherapy agent with the greatest degree of emetic risk.[42] Likewise, choice of antiemetic treatment should be based on the agent with the greatest degree of emetic risk in patients receiving both chemotherapy and radiotherapy. The preferred type-3 serotonin (5-HT_3) receptor antagonist for patients receiving moderately emetogenic chemotherapy (MEC) is palonosetron (Aloxi; day 1), and it should be combined with a corticosteroid (days 1 through 3). They also recommend that all patients who receive highly emetogenic chemotherapy (HEC), including anthracycline plus cyclophosphamide, should be offered a 3-drug combination of a NK_1 receptor antagonist (day 1 or days 1 through 3 based on formulation), a 5-HT_3 receptor antagonist (day 1), and dexamethasone (days 1 through 3 or 4). One 5-HT_3 receptor antagonist is not preferred over another. A single dose of dexamethasone is recommended for patients using low emetogenic agents. ASCO recommends both dexamethasone and a 5-HT_3 receptor antagonist for patients receiving high-dose chemotherapy. Those receiving highly emetogenic radiation therapy should receive a 5-HT_3 receptor antagonist before each fraction and a 5-day course of dexamethasone. A 5-HT_3 receptor antagonist prior to each fraction also is recommended before moderately emetogenic radiation therapy, but in this case, a 5-day course of dexamethasone is optional. Preferred 5-HT_3 receptor antagonists include granisetron and ondansetron (oral or intravenous). The addition of a benzodiazepine or dopamine agonist or substitution of high-dose intravenous metoclopramide for the 5-HT_3 receptor antagonist may be considered in patients with emesis or nausea despite optimal prophylaxis. Optimal treatment should be used with initial chemotherapy to limit anticipatory nausea and vomiting.

A focused update to the ASCO guidelines published online in 2015 reaffirms that all patients who receive HEC, including anthracycline plus cyclophosphamide, should be offered a 3-drug combination described above.[43] They further suggest that the oral combination of netupitant and palonosetron (Akynzeo) plus dexamethasone is an additional treatment option in this setting, as it was not available at the time of the 2011 guidelines. Other recommendations were unchanged. Rolapitant (Varubi) was not addressed in these guidelines.

The v2.2015 National Comprehensive Cancer Network (NCCN) guidelines state that the choice of antiemetic should be based on emetic risk of the chemotherapy, prior experience with antiemetics, as well as patient factors.[44] Furthermore, the guidelines state that antiemetic therapy should be initiated prior to the start of chemotherapy to provide maximal protection against chemotherapy-induced emesis. In addition, the antiemetic therapy should be continued for the same timeframe as the

duration of the emetic activity of the chemotherapeutic agent being used. The guidelines identify emesis prevention treatment options for high, moderate, low, and minimal emetic risk IV chemotherapy, oral chemotherapy, as well as breakthrough treatment for chemotherapy-induced N/V. To prevent acute and delayed emesis in patient receiving intravenous HEC, NCCN recommends a 3-drug combination of a NK_1 receptor antagonist (aprepitant [Emend], fosaprepitant [Emend], or rolapitant [Varubi]; duration based on formulation), a 5-HT_3 receptor antagonist (day 1), and dexamethasone (days 1 through 4). Equivalent alternatives to this 3-drug regimen include netupitant/palonosetron (Akynzeo) with dexamethasone and olanzapine containing regimens (olanzapine, palonosetron [Aloxi], and dexamethasone). To prevent acute and delayed emesis in patient receiving intravenous MEC, NCCN recommends a 5-HT_3 receptor antagonist and steroid with or without a NK_1 receptor antagonist (aprepitant, fosaprepitant, or rolapitant). NCCN does not specify one 5-HT_3 receptor antagonist over another (or route/formulation). Equivalent alternatives to this 3-drug regimen include netupitant/palonosetron with dexamethasone and olanzapine containing regimens (olanzapine, palonosetron, and dexamethasone). For low emetogenic risk chemotherapy, dexamethasone, metoclopramide (Reglan), prochlorperazine (Compro), or an oral 5-HT_3 receptor antagonist may be used. There is no routine prophylaxis for patients who receive minimal emetic risk IV chemotherapy. For patients who receive oral chemotherapy where prophylaxis is recommended, an oral 5-HT_3 antagonist should be initiated prior to chemotherapy. Conversely, for patients who receive oral chemotherapy where no prophylaxis or as needed prophylaxis is recommended, patients may receive alternative agents like metoclopramide (Reglan) or prochlorperazine (Compro). If N/V persists, then an oral 5-HT_3 antagonist could be initiated. Finally, for breakthrough treatment of chemotherapy-induced N/V, the general principle is to add one agent from a different class, as needed, to the existing regimen (e.g., antipsychotic, benzodiazepine, cannabinoid, dopamine receptor antagonist, phenothiazine, 5-HT_3 antagonist, or corticosteroid). Based on response to the breakthrough treatment, the antiemetic therapy is adjusted and/or modified. Details on dosing and duration are dependent on the formulation selected and are detailed in the NCCN guidelines. Overall, minimal changes were made with this new guideline; however, this version addressed rolapitant, and palonosetron is no longer a preferred 5-HT_3 receptor antagonist.

Motion sickness is the result of a conflict between the various senses in regard to motion.[45] The semicircular canals and otoliths in the inner ear sense angular and vertical motion, while the eyes and the proprioceptors determine the body's position in space. When signals received by the eyes or the proprioceptors do not match those being transmitted by the inner ear, motion sickness occurs. It can occur in either the presence or absence of actual motion, such as when viewing a slide through a microscope. Symptoms include nausea, vomiting, pallor, sweating, and often a sense of impending doom. There are both non-pharmacologic and pharmacologic interventions for the prevention or management of motion sickness. None are ideal, and the medications typically cause drowsiness or similar adverse effects.

Nausea and vomiting of pregnancy "morning sickness," which can occur at any time of day, can affect pregnant women with varying symptoms from nausea to severe vomiting. Lifestyle changes for women with nausea and vomiting of pregnancy include rest, avoiding nauseating stimuli, eating small, frequent low fat meals that are low in spices.[46] According to the American College of Obstetrician and Gynecologist (ACOG) and Association of Professors of Gynecology and Obstetrics, the treatment of N/V of pregnancy with over-the-counter vitamin B6 (pyridoxine) or vitamin B6 plus doxylamine have been first-line recommendations for many years.[47,48] Other medications have been used off-label such as ondansetron, dimenhydrinate, metoclopramide and promethazine, all of which are pregnancy category

B or C. Diclegis, a fixed-dose combination of the antihistamine doxylamine 10 mg plus pyridoxine 10 mg, is the first FDA-approved, pregnancy category A delayed-release combination medication for the treatment of N/V of pregnancy. Bendectin®, which contained the same combination of products as Diclegis, was voluntarily withdrawn by the manufacturer years ago due to allegations that it caused birth defects.[49] Studies have never proven this claim and, subsequently, the FDA stated that the product was not withdrawn for reasons of safety or effectiveness.

PHARMACOLOGY[50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72]

NK_1 receptor antagonists [aprepitant (Emend), fosaprepitant (Emend for Injection), rolapitant (Varubi)]

Aprepitant (Emend) exerts its main antiemetic action by occupying brain substance P-NK_1 receptors. This receptor pathway regulates the behavioral responses to a range of noxious and stressful stimuli. Expression in the brainstem emetic nuclei has implicated substance P in the control of vomiting.[73] Aprepitant has little or no affinity for 5-HT_3, dopamine, or corticosteroid receptors. Fosaprepitant (Emend for injection) is a prodrug of aprepitant and is quickly converted to aprepitant when administered intravenously.

Rolapitant (Varubi) is a selective and competitive antagonist of substance P-NK_1 receptors and also has little or no affinity for other receptors.

5-HT_3 antagonists [dolasetron (Anzemet), granisetron, granisetron transdermal (Sancuso), ondansetron (Zofran, Zuplenz), palonosetron (Aloxi)]

Dolasetron (Anzemet), granisetron (Sancuso), ondansetron (Zofran, Zuplenz), and palonosetron (Aloxi) selectively block 5-HT_3 receptors. While the mechanism of action of these drugs has not been fully elucidated, they are not D_2 receptor antagonists. Serotonin receptors of the 5-HT_3 type are found centrally in the chemoreceptor trigger zone (CTZ) and peripherally at vagal nerve terminals in the intestines. It has not been determined whether the antiemetic action of the 5-HT_3 antagonists is mediated centrally, peripherally, or a combination of both sites. N/V during chemotherapy appears to be associated with release of serotonin from the enterochromaffin cells of the small intestine. The released serotonin may stimulate vagal afferents through the 5-HT_3 receptors and initiate the vomiting reflex.

Combination products [netupitant/palonosetron (Akynzeo)]

Netupitant/palonosetron (Akynzeo) contains netupitant, an NK_1 receptor antagonist and palonosetron, 5-HT_3 antagonist. It exerts its effect by occupying brain substance P-NK_1 receptors and selectively blocking 5-HT_3 receptors as mentioned above in the NK_1 receptor antagonist and 5-HT_3 antagonists sections.

Cannabinoids [dronabinol (Marinol), nabilone (Cesamet)]

Dronabinol (Marinol) and nabilone (Cesamet) act on the cannabinoid receptors (CB1 and CB2) in the brain.[74] These receptors are believed to regulate nausea and vomiting. Like most cannabinoids, these agents have complex effects on the central nervous system (CNS) and may even exert central sympathomimetic activity.

Antidopaminergics [metoclopramide (Reglan, Metozolv ODT)]

Metoclopramide (Reglan, Metozolv ODT) aids in gastric motility, increasing emptying and intestinal transit. Antiemetic properties are due to its effects on central and peripheral dopamine receptors. It blocks dopaminergic activity to the medullary chemoreceptor trigger zone.

Phenothiazines [promethazine (Phenergan), prochlorperazine (Compro)]

The phenothiazines block postsynaptic dopaminergic receptors in the brain, including the CTZ. This mechanism contributes to depression of the reticular activating system and affects basal metabolism, body temperature, wakefulness, vasomotor tone, and emesis. Promethazine also has both antihistaminic and anticholinergic properties.

Antihistamines [dimenhydrinate (Dramamine OTC), diphenhydramine (Benadryl), meclizine (Antivert, Univert), doxylamine/pyridoxine (Diclegis)]

Histaminergic (H1) antagonists act on the vomiting center and vestibular pathways making them effective in the prevention and treatment of motion sickness induced N/V. The mechanism of action of the antihistamine doxylamine and the vitamin B6 (pyridoxine) combination (Diclegis) is unknown for the treatment of N/V of pregnancy.

Anticholinergics [scopolamine (Transderm-Scop)]

It is suggested that scopolamine (Transderm-Scop) exerts its activity in the central nervous system by blocking activity to the vomiting center and vestibular nuclei.

PHARMACOKINETICS[75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97]

Antiemetics					
Drug	**Bioavailability (%)**	**Half life (t1/2) (hr)**	**Metabolites**	**Excretion (%)**	
NK_1 receptor antagonist					
aprepitant (Emend)	60–65	9–13	7, weakly active	urine: 57 feces: 45	
fosaprepitant (Emend for injection)	--	9–13	prodrug converted to aprepitant	urine: 57 feces: 45	
rolapitant (Varubi)	--	169 – 183	M19, active	urine: 14.2 feces: 73	
5-HT_3 antagonists					
dolasetron (Anzemet)	75 (oral)	8.1 (oral) 7.3 (IV)	hydrodolasetron, active	oral	urine: 61 feces: 39
				IV	urine: 53
granisetron	--	6.2 (oral) 4.91–8.95 (IV)	yes, activity questionable	oral	urine: 48 feces: 38
				IV	urine: 49 feces: 34
granisetron transdermal (Sancuso)	--	N/A; 66% is released from patch over 7 days	yes	urine: 49 feces: 34	
ondansetron (Zofran, Zuplenz)	56 (oral)	3.1–6.2 (oral) 2.5–6.7 (IV)	yes, none significant	urine: 5	
palonosetron (Aloxi)	--	≈40	yes	feces: 5 to 8 urine: 80	
Combination products					
netupitant/palonosetron (Akynzeo)	97	80	yes, weakly active	feces: 5 to 8 urine: 85 to 93	
Cannabinoids					
dronabinol (Marinol)	10–20	25–36	yes, 1 active	urine: 10–15 feces: 50	
nabilone (Cesamet)	5–20	2–35	yes, active and inactive	urine: 24 feces: 60	
Antidopaminergics					
metoclopramide (Metozolv ODT)	65–95	5–6	none	urine: 85 feces:2	
metoclopramide (Reglan)					
Antihistamines					
doxylamine/pyridoxine (Diclegis)	--	doxylamine – 12.5 pyridoxine – 5	doxylamine – yes pyridoxine – prodrug	--	

Pharmacokinetics (continued)

Antiemetics				
Drug	**Bioavailability (%)**	**Half life (t1/2) (hr)**	**Metabolites**	**Excretion (%)**
Others				
phosphorated carbohydrate solution (Emetrol OTC)	--	--	--	--
trimethobenzamide (Tigan)	60–100	7–9	yes, 1 active	urine:30–50
Antivertigo Agents				
Antihistamines				
dimenhydrinate (Dramamine OTC)	--	3.5	yes, active	--
diphenhydramine (Benadryl)	65–100	2.4–9.3	yes, 5 active	urine: 50–75
meclizine (Antivert, Bonine, Univert)	--	6	yes, 1 active	--
Phenothiazines				
prochlorperazine (Compro)	12.5	6–10 (single dose) 14–22 (repeat dosing)	yes; 1 active	--
promethazine (Phenergan)	low	10-14	yes, 1 active	--
Anticholinergics				
scopolamine (Transderm-Scop)	--	--	yes	urine: 34

CONTRAINDICATIONS/WARNINGS[98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113,114,115,116,117,118,119,120]

Aprepitant and fosaprepitant (Emend) are contraindicated in patients who are hypersensitive to any component of the product. Known hypersensitivity reactions include flushing, erythema, dyspnea, and anaphylactic reactions. Aprepitant and fosaprepitant should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Inhibition of CYP3A4 by aprepitant or fosaprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions. Proteinuria has been reported in 6.8% of patients receiving aprepitant in clinical trials. Rolapitant (Varubi) is contraindicated in patients taking the CYP2D6 substrate, thioridazine. There is also a warning regarding the interaction between rolapitant and other CYP2D6 substrates with a narrow therapeutic index. The inhibitory effect of rolapitant on CYP2D6 can last 7 days or longer. Therefore, rolapitant should be avoided in patients taking pimozide. An increase in plasma concentrations of thioridazine, pimozide or other CYP2D6 substrates can result in QT prolongation.

There is no clinical data for the use of aprepitant in patients with hepatic impairment and, therefore, caution should be used when administering aprepitant to these patients.

5-HT_3 receptor antagonists are contraindicated in patients with known hypersensitivity to the drug or any of its components. Cross hypersensitivity reactions have been reported in patients who received

other selective $5HT_3$ receptor antagonists. These reactions have not been seen with dolasetron (Anzemet).

5-HT_3 receptor antagonists should be administered with caution in patients who have or may develop arrhythmias or prolongation of cardiac conduction intervals, particularly QTc. Electrocardiogram (ECG) changes have occurred in patients using ondansetron (Zofran, Zuplenz) and dolasetron (Anzemet), including QT interval prolongation and Torsades de Pointes; therefore, the use of ondansetron and dolasetron should be avoided in patients with congenital long QT syndrome. ECG monitoring should also be performed in patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias, or patients taking other medications, which increase the risk of QT prolongation.

Serotonin syndrome has been reported with 5-HT_3 receptor antagonists (including netupitant/palonosetron due to the palonosetron component) alone but particularly with concomitant use of serotonergic drugs. Patients should be monitored for the emergence of serotonin syndrome, especially with concomitant use of 5-HT_3 receptor antagonists and other serotonergic drugs.

Hypersensitivity reactions, including anaphylaxis, have been reported in patients receiving netupitant/palonosetron (Akynzeo) with or without known hypersensitivity to other 5-HT_3 receptor antagonists, alone but also with concomitant serotonergic drugs.

Granisetron and ondansetron (Zofran, Zuplenz) do not stimulate gastric or intestinal peristalsis. They should not be used instead of nasogastric suction. Use in patients following abdominal surgery or in chemotherapy-induced N/V may mask a progressive ileus and/or gastric distention. Granisetron injection contains benzyl alcohol and has been associated with serious adverse reactions and death, especially in neonates.

Dolasetron solution administered intravenously is contraindicated in adult and pediatric patients for the prevention of N/V associated with initial and repeat courses of emetogenic cancer chemotherapy due to dose dependant QT prolongation. Dolasetron should be used with caution in patients with hypomagnesium, hypokalemia, or congenital long QT syndrome. Hypomagnesium and hypokalemia should be corrected prior to beginning dolasetron therapy and monitored thereafter. Dolasetron (Anzemet) may cause dose dependent prolongation of the PR, QRS, and QT interval and second and third degree atrioventricular block, cardiac arrest, and serious ventricular arrhythmias may occur.

Patients with phenylketonuria should be informed that ondansetron orally disintegrating tablets (Zuplenz) contain < 0.03 mg phenylalanine in both the 4 mg and 8 mg tablets.

The concomitant use of apomorphine with ondansetron is contraindicated based on reports of profound hypotension and loss of consciousness with coadministration.

Dronabinol (Marinol) is contraindicated in patients with any known sensitivities to dronabinol, cannabinoid oil, sesame oil, or any other of its ingredients. Nabilone (Cesamet) is contraindicated in patients with a hypersensitivity to any cannabinoid.

Adverse psychiatric effects can persist for 48 to 72 hours following discontinuation of nabilone. Cautious use of both cannabinoids in patients with current or previous psychiatric disorders (e.g., manic depression, depression, and schizophrenia) is recommended. Nabilone can have adverse effects on the central nervous system including dizziness, drowsiness, euphoria, disorientation, depression, hallucinations, anxiety, and psychosis.

Cautious use of the cannabinoids is recommended also in patients with a history of substance abuse and dependence.

Although a causal relationship has not been established, dronabinol may lower the seizure threshold; therefore, it should be used with caution in patients with a history of seizure disorder.

Dronabinol and nabilone should be used with caution in patients with cardiac disorders due to occasional hypotension, possible hypertension, syncope, or tachycardia.

Patients receiving treatment with dronabinol and nabilone should be specifically warned not to drive, operate machinery, or engage in any hazardous activity while receiving dronabinol and nabilone.

Metoclopramide (Reglan, Metozolv ODT) is contraindicated in patients with pheochromocytoma because the drug may cause a hypertensive crisis, probably due to release of catecholamines from the tumor. Metoclopramide is contraindicated in patients with known sensitivity or intolerance to the drug. Metoclopramide should not be used in epileptics or patients receiving other drugs that are likely to cause extrapyramidal reactions, since the frequency and severity of seizures or extrapyramidal reactions may be increased. Neonates, infants, children, and adolescents are more likely to experience extrapyramidal side effects.

Metoclopramide should not be used in patients with conditions in which stimulation of the gastrointestinal track is of concern.

Mental depression has occurred with metoclopramide in patients with and without prior history of depression.

Patients with pre-existing Parkinson's disease should be given metoclopramide cautiously, if at all, since such patients may experience exacerbation of parkinsonian symptoms when taking metoclopramide.

Metoclopramide has a black box warning for chronic long-term or high-dose use that can lead to increased risk of tardive dyskinesia, involuntary and repetitive movements of the body, even after the drug has been discontinued. Treatment with metoclopramide for longer than 12 weeks is not recommended

There have been rare reports of an uncommon, but potentially fatal, symptom complex sometimes referred to as neuroleptic malignant syndrome (NMS) associated with metoclopramide.

Patients with cirrhosis or congestive heart failure may be at risk for fluid retention and volume overload due to an increase in plasma aldosterone. If fluid retention or volume overload occurs, metoclopramide therapy should be discontinued. .

Trimethobenzamide (Tigan) injection is contraindicated in pediatric patients and in patients with known hypersensitivity to trimethobenzamide. Trimethobenzamide may produce drowsiness. Patients should not operate motor vehicles or other dangerous machinery until their individual responses have been determined. In disorders such as acute febrile illness, encephalitis, gastroenteritis, dehydration, and electrolyte imbalance, caution should be exercised in administering trimethobenzamide, particularly to patients who have recently received other CNS-acting agents (phenothiazines, barbiturates, belladonna derivatives). The antiemetic effects of trimethobenzamide may obscure the cause of vomiting in various disorders, such as appendicitis, and may mask the symptoms of overdosage of other drugs.

Promethazine (Phenergan) and prochlorperazine (Compro) are contraindicated in comatose states, and in individuals known to be hypersensitive or to have had an idiosyncratic reaction to phenothiazines. Promethazine tablets and prochlorperazine should be used cautiously in persons with cardiovascular disease or with impairment of liver function. Prochlorperazine should be used cautiously in patient populations with pheochromocytoma as prochlorperazine-induced buildup of neurotransmitters can result in a cardiotoxic effect.

Doxylamine/pyridoxine (Diclegis) is contraindicated in patients hypersensitive to doxylamine succinate, other ethanolamine derivative antihistamines, or pyridoxine hydrochloride. Doxylamine/pyridoxine is contraindicated in concomitant use with monoamine oxidase (MAO) inhibitors due to an intensification and prolongation of central nervous system effects. Doxylamine/pyridoxine may cause somnolence and patients should avoid engaging in activities requiring complete mental alertness, such as driving, until cleared to do so by their healthcare provider (HCP). Due to the anticholinergic antihistamine component, it is not recommended to be used with CNS depressants, including alcohol, and should be used with caution in patients with asthma, increased intraocular pressure, narrow angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, and urinary bladder-neck obstruction.

Scopolamine (Transderm-Scop) is contraindicated in persons who are hypersensitive to the drug scopolamine or to other belladonna alkaloids, or to any ingredient or component in the formulation or delivery system, or in patients with angle-closure (narrow angle) glaucoma.

DRUG INTERACTIONS[121,122,123,124,125,126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142,143]

aprepitant (Emend) and fosaprepitant dimeglumine (Emend for Injection), and rolapitant (Varubi)

Aprepitant and fosaprepitant (Emend) should be used with caution in patients receiving concomitant medicinal products, including chemotherapy agents, which are primarily metabolized through CYP3A4. The effect of aprepitant on the pharmacokinetics of orally administered CYP3A4 substrates is expected to be greater than its effect on the pharmacokinetics of intravenous (IV) CYP3A4 substrates. Weak inhibition of CYP enzymes by 40 mg doses of aprepitant is not expected to affect concentration of other drugs to a significant degree. Higher aprepitant doses and repeat doses may produce a clinically significant effect. Moderate inhibition of CYP3A4 by aprepitant 125/80 mg and weak inhibition of CYP3A4 by fosaprepitant 150 mg may result in increased plasma concentrations of these concomitant medicinals. Coadministration of aprepitant or fosaprepitant with drugs that inhibit CYP3A4 activity (e.g., ketoconazole, itraconazole, nefazodone, diltiazem, clarithromycin, ritonavir, nelfinavir) may result in increased plasma concentrations of aprepitant. If concomitantly used with CYP3A4 inducers (e.g., rifampin, carbamazepine, and phenytoin), aprepitant concentrations may be reduced and may result in decreased aprepitant efficacy. CYP2C9 metabolism may be induced by aprepitant.

Coadministration of aprepitant or fosaprepitant with warfarin may result in a clinically significant (14%) decrease in international normalized ratio (INR). In patients on warfarin, INR should be closely monitored at 7 to 10 days following initiation of the 3-day regimen of aprepitant with each chemotherapy cycle or after a single aprepitant 40 mg dose for the prevention of N/V.

Coadministration with fosaprepitant or aprepitant may reduce the efficacy of hormonal contraceptives, such as oral contraceptives, transdermal patches, implants, and certain interuterine

devices (IUDs), during and for 28 days following the last dose of either fosaprepitant or aprepitant. Alternative or back-up methods of contraception should be used during treatment with and for 1 month following the last dose of fosaprepitant or aprepitant.

Because administration of aprepitant or fosaprepitant with dexamethasone or methylprednisolone approximately doubles the area-under-the-curve (AUC) of the corticosteroid, doses of corticosteroid should be reduced by 50% when co-administered with aprepitant.[144]

Chronic continuous use of fosaprepitant for prevention of N/V is not recommended because it has not been studied and because the drug interaction profile may change during chronic continuous use.

Concomitant use of benzodiazepines with aprepitant or fosaprepitant may increase benzodiazepine concentrations; therefore, close monitoring and potential benzodiazepine dose reduction may be warranted.

Concomitant use of rolapitant (Varubi) with chronic administration of a strong CYP3A4 inducer (e.g., rifampin) is not recommended due to potential reduced efficacy of rolapitant.

Increased concentrations of Breast-Cancer-Resistance Protein (BCRP) substrates (e.g., methotrexate, topotecan), CYP2D6 substrates, or P-gp substrates (e.g., digoxin) may result in potential adverse reactions. Monitor for adverse reactions if concomitant use cannot be avoided.

5-HT_3 receptor antagonists

Dolasetron (Anzemet), granisetron (Sancuso), palonosetron (Aloxi), and ondansetron (Zofran, Zuplenz) are metabolized by various CYP450 enzymes; however, due to the variety of enzymes involved, no clinically significant drug interactions have been identified at this time.

In patients treated with potent inducers of CYP3A4 (e.g., phenytoin, carbamazepine, and rifampin), the clearance of ondansetron was significantly increased, and ondansetron blood concentrations were decreased. However, on the basis of available data, no dosage adjustment for ondansetron is recommended for patients on these drugs. Due to granisetron being metabolized by the cytochrome P-450 system, taking this medication with enzyme inducers or inhibitors could affect the clearance of granisetron.

The concomitant use of ondansetron and tramadol may decrease the analgesic effectiveness of tramadol.

Blood levels of hydrodolasetron increased 24% when dolasetron was coadministered with cimetidine (nonselective inhibitor of CYP450) for 7 days and decreased 28% with coadministration of rifampin (potent inducer of CYP450) for 7 days. Blood levels of hydrodolasetron decreased approximately 27% when intravenous dolasetron was administered with atenolol.

Caution should be exercised when dolasetron is coadministered with drugs that prolong ECG intervals and/or cause hypokalemia or hypomagnesemia including those used in chemotherapy and surgery.

QT prolongation has been reported with granisetron. The use of granisetron in patients concurrently treated with drugs known to prolong the QT interval and/or is arrhythmogenic may result in clinical consequences.

Combination Products

Netupitant/palonosetron (Akynzeo) contains netupitant, a moderate inhibitor of cytochrome CYP3A4. Netupitant/palonosetron should be used with caution in patients receiving concomitant medications that are primarily metabolized through CYP3A4 because the plasma concentrations of the medication can increase. Netupitant is also mainly metabolized by CYP3A4. Avoid concomitant use of netupitant/palonosetron in patients who are chronically using a strong CYP3A4 inducer (e.g., rifampin, carbamazepine, phenytoin). A strong CYP3A4 inducer can decrease the efficacy of netupitant/palonosetron by substantially reducing plasma concentrations of the netupitant component. Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, nefazodone, diltiazem, clarithromycin, ritonavir, nelfinavir) can significantly increase the systemic exposure to the netupitant component of netupitant/palonosetron but no dosage adjustment is necessary.

A 2-fold increase in the systemic exposure of dexamethasone was observed 4 days after a single dose of netupitant and the duration of the effect was not studied beyond 4 days. Administer a reduced dose of dexamethasone with netupitant/palonosetron.

When administered with netupitant, the systemic exposure to midazolam was significantly increased. Consider the potential effects of increased plasma concentrations of midazolam or other benzodiazepines metabolized via CYP3A4 (e.g., alprazolam, triazolam) when administering these drugs with netupitant/palonosetron.

Serotonin syndrome has been described following the concomitant use of 5-HT_3 receptor antagonists and other serotonergic drugs, including selective serotonin reuptake inhibitors and serotonin and noradrenaline reuptake inhibitors.

Cannabinoids

Both of the cannabinoids, dronabinol (Marinol) and nabilone (Cesamet), are highly protein bound and may displace other highly protein bound drugs. Examples include tricyclic antidepressants, amphetamines, barbiturates, benzodiazepines, fluoxetine, theophylline, and others. A change in dosage of the concomitant drug may be necessary. Consult prescribing information for dosage recommendations.

Dronabinol and nabilone should be used with caution when used concomitantly with sedatives, hypnotics, or other psychoactive medications due to the potential for synergistic CNS effects.

Nabilone should not be taken with alcohol, sedatives, hypnotics, or other psychoactive substances because these substances can potentiate its central nervous system effects.

Antidopaminergics

Anticholinergic drugs and narcotic analgesics antagonize the effects of metoclopramide (Reglan, Metozolv ODT) on gastrointestinal motility. Additive sedative effects can occur when metoclopramide is given with alcohol, sedatives, hypnotics, narcotics, or tranquilizers.

Metoclopramide has been shown to release catecholamines in patients with essential hypertension. It is suggested that it should be used cautiously, if at all, in patients taking monoamine oxidase (MAO) inhibitors.

Metoclopramide is a central dopamine antagonist and may affect the actions of dopamine agonists and COMT inhibitors.

Metoclopramide should not be used with other medications known to cause extrapyramidal reactions, such as antidepressant, antipsychotic, and neuroleptic agents.

Absorption of drugs from the stomach may be diminished by metoclopramide (e.g., digoxin), whereas the rate and/or extent of absorption of drugs from the small bowel may be increased (e.g., acetaminophen, tetracycline, levodopa, ethanol, cyclosporine).

Metoclopramide will influence the delivery of food to the intestines and thus the rate of absorption; therefore, insulin dosage or timing of dosage may require adjustment.

Phenothiazines

Prochlorperazine (Compro) may diminish the effect of dopamine agonists (antiparkinsons agents). Prochlorperazine may enhance the toxic effects of antipsychotics and enhance CNS depressant effects of opioids, barbiturates, and other CNS agents. Promethazine (Phenergan) is a major substrate of CYP2D6; therefore, monitor therapy with CYP2D6 inhibitors or inducers. Avoid combination with metoclopramide (Reglan, Metozolv ODT) or serotonin modulators.

Phenothiazines have been reported to prolong the QT interval. Taking phenothiazines with other medications known to prolong QT intervals should be avoided.

Caution should be used when phenothiazines are used with other drugs with antimuscarinic activity as side effects may be potentiated.

Caution should be used when phenothiazines are used with CNS depressants such as anxiolytics, sedatives, and hypnotics, as additive depressive CNS effects could occur.

Phenothiazines can lower the seizure threshold and dose adjustments of anticonvulsants may be needed.

Antihistamines

Dimenhydrinate (Dramamine OTC), diphenhydramine (Benadryl), meclizine (Antivert, Bonine), and doxylamine/pyridoxine (Diclegis) may enhance the toxic effects of CNS depressants and anticholinergics. Doxylamine/pyridoxine is contraindicated in concomitant use with MAO inhibitors due to an intensification and prolongation of CNS effects. There are no known drug interactions with the vitamin B6 component of doxylamine/pyridoxine. Diphenhydramine moderately inhibits CYP2D6; therefore, therapy with tramadol, codeine, tamoxifen, and nebivolol should be monitored.

Anticholinergics

The absorption of oral medications may be decreased during the concurrent use of scopolamine (Transderm-Scop) because of decreased gastric motility and delayed gastric emptying. Scopolamine should be used with care in patients taking other drugs that are capable of causing CNS effects, such as sedatives, tranquilizers, or alcohol. Special attention should be paid to potential interactions with drugs having anticholinergic properties (e.g., other belladonna alkaloids, antihistamines [including meclizine], tricyclic antidepressants, and muscle relaxants).

ADVERSE EFFECTS[145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167]

Antiemetic Drug	Hepatic function abnormalities	Tachycardia	Headache	Euphoria	Hypotension	Diarrhea	Fatigue	Nausea
NK_1 receptor antagonist								
aprepitant (Emend)	3–6	>0.5	5–13.2	nr	0.5–5.7	7.6–10.3	4.7–17.8	5.8–12.7
fosaprepitant (Emend for injection)	1.1–2.8	nr	2.2	<1	nr	1.1	1.4–2.9	<1
rolapitant (Varubi)	nr	nr	nr	nr	nr	nr	nr	nr
5-HT_3 antagonists								
dolasetron (Anzemet)	<1	2.2–3	7–22.9	nr	<2–5.3	2.1–5.3	2.6–5.7	nr
granisetron	5–6 (oral) 2.8–5.6 (IV)	nr (oral) nr (IV)	14–21 (oral) 8.6–14 (IV)	nr (oral) nr (IV)	reported (oral) reported (IV)	4–9 (oral) 3.4 (IV)	nr (oral) nr (IV)	20
granisetron transdermal (Sancuso)	reported	nr	<1	nr	reported	reported*	nr	reported
ondansetron (Zofran, Zuplenz)	1–2 (oral) 5 (IV)	reported (oral and IV)	11–27 (oral) 17 (IV)	nr (oral and IV)	5 (oral) reported (IV)	3–7 (oral) 16 (IV)	9–13 (oral) nr (IV)	nr (oral and IV)
palonosetron (Aloxi)	<1	1	9	<1	1	1	<1	nr
Combination products								
netupitant/palonosetron (Akynzeo)	<1	nr	9	nr	nr	nr	7	nr
Cannabinoids								
dronabinol (Marinol)	<1	>1	<1	3–10	0.3–1	0.3–1	nr	3–10

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all-inclusive. nr = not reported.

* Constipation is the predominant adverse effect associated with granisetron transdermal (Sancuso), occurring at a rate of 5.4%.

Adverse Effects (continued)

Antiemetic Drug	Hepatic function abnormalities	Tachycardia	Headache	Euphoria	Hypotension	Diarrhea	Fatigue	Nausea
Cannabinoids (continued)								
nabilone (Cesamet)	nr	reported	6–7	11–38	8	reported	reported	4
Antidopaminergics								
metoclopramide (Metozolv ODT)	reported	reported	5.2	nr	reported	reported	2.1	4.2
metoclopramide (Reglan)	reported	reported	reported	nr	reported	reported	10	reported
Antihistamines								
doxylamine/ pyridoxine (Diclegis)	nr	nr	nr	nr	nr	nr	nr	nr
Other								
trimethobenzamide (Tigan)	nr	nr	reported	nr	reported	reported	nr	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all-inclusive. nr = not reported.

Doxylamine/ pyridoxine (Diclegis): The most common adverse effect occurring in ≥ 5% of patients reported was somnolence (14.3%). In post marketing, adverse effects that occurred include dyspnea, palpitations, tachycardia, vertigo, visual disturbances, abdominal distension, anxiety, dysuria, and rash. Frequency could not be accurately determined since these are reported voluntarily.

Adverse Effects (continued)

Antivertigo Agents	Drowsiness	Xerostomia	Tachycardia	Rash	Blurred Vision	Urinary Retention
Antihistamines						
dimenhydrinate (Dramamine OTC)	reported	reported	reported	reported	reported	reported
diphenhydramine (Benadryl)	reported	reported	reported	reported	reported	reported
meclizine (Antivert, Bonine, Univert)	31	16.7	reported	nr	reported	reported
Phenothiazines						
prochlorperazine (Compro)	reported	reported	reported	nr	reported	reported
promethazine (Phenergan)	reported	reported	reported	nr	reported	reported
Anticholinergics						
scopolamine (Transderm-Scop)	17	67	reported	reported	reported	reported

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all-inclusive. nr = not reported.

SPECIAL POPULATIONS[168,169,170,171,172,173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190]

Pediatrics

Prescribing information states that oral ondansetron (Zofran) can be used for patients older than 4 years old. However, little information is available about oral ondansetron dosing in pediatric patients 4 years of age or younger. There is no experience with the use of oral ondansetron 24 mg dosage in pediatric patients. There is no experience with the use of oral ondansetron in the prevention of radiation-induced or post-operative N/V in pediatric patients.

Information is lacking regarding the use of injectable ondansetron (Zofran) in surgical patients younger than 1 month of age and use in cancer patients younger than 6 months of age. The safety and effectiveness of ondansetron soluble film (Zuplenz) has been established for the prevention of N/V associated with moderately emetogenic chemotherapy in patients 4 years of age and older. Otherwise, the safety and effectiveness of this product in children have not been evaluated.

Dolasetron (Anzemet) tablets are indicated for use in patients 2 years of age and older in the prevention of post-operative N/V and the prevention of chemotherapy-induced N/V. Dolasetron injection is contraindicated in pediatric patients for the prevention of N/V related to initial and repeat courses of emetogenic chemotherapy. Safety and effectiveness of injectable dolasetron in pediatric patients (2 years and older) for prevention and treatment of post-operative N/V is based on pharmacokinetic studies and efficacy data in adults. Safety and effectiveness of injectable dolasetron in pediatric patients less than 2 years of age have not been established.

In a randomized, placebo-controlled, double-blind trial, oral dolasetron and ondansetron were compared in preventing post-operative N/V in 150 children after various surgical operations.[191] Children were assigned randomly to 1 of 3 groups to receive dolasetron 1.8 mg/kg, ondansetron 0.15 mg/kg, or a placebo. All children received methylene blue capsules orally as an indicator before the induction of anesthesia. Post-operative contamination of the mouth and the endotracheal tube by methylene blue, and post-operative N/V were recorded for 24 hours. In the 1-hour period after the operation, there were no differences between the groups. During the period 1 to 24 hours after surgery, dolasetron was significantly better than placebo (incidence: 16% with dolasetron versus 48% with placebo for overall nausea and vomiting). Over the entire 24 hours, both dolasetron and ondansetron were significantly better than placebo (incidence: 32% with dolasetron and 48% with ondansetron versus 78% with placebo for overall nausea and vomiting). There were no significant differences between dolasetron and ondansetron, and no important adverse events were reported.

Safety and efficacy of oral granisetron and granisetron transdermal (Sancuso) have not been established for pediatric patients. Granisetron injectable may be used for chemotherapy-induced N/V in pediatric patients 2 to 16 years of age. Granisetron may be effective in patients older than 4 years old, according to limited randomized, controlled trials for post-operative N/V.[192,193,194] There is no experience with oral granisetron in the prevention of radiation-induced N/V in pediatric patients.

Safety and effectiveness of use of palonosetron (Aloxi) in patients less than the age of 18 years have not been established.

A Cochrane review of the use of 5-HT_3 receptor antagonists in pediatrics found that additional research was needed to make any conclusions, but did find that the addition of dexamethasone to one of these agents may be beneficial in HEC (pending a risk/benefit assessment).[195]

Aprepitant (Emend) is approved for prevention of N/V secondary to moderately and highly emetogenic chemotherapy in patients 12 years of age and older and in those less than 12 years who weigh at least 30 kg. However, it is not approved in pediatrics for the prevention of post-operative N/V.

A phase 3, multicenter, randomized, double-blind study compared the efficacy aprepitant to placebo (both with standard therapy) in patients ages 6 months to 17 years scheduled to receive MEC or HEC (n=307).[196] Patients were assigned to aprepitant (3 mg/kg to a maximum of 125 mg) plus ondansetron on day 1 and aprepitant (2 mg/kg to a maximum of 80 mg) on days 2 and 3 or placebo plus ondansetron on day 1 and placebo on days 2 and 3. All doses were weight based (using either aprepitant oral capsules or aprepitant oral suspension). The primary efficacy endpoint was the proportion of patients who achieved complete response (defined as no vomiting, retching, or use of rescue medication) during the delayed phase (25 to 120 hours) after chemotherapy initiation. Fifty one percent (77/152) of patients in the aprepitant group compared to 26% (39/150) in the placebo/control group achieved a complete response ($p<0.0001$). Notably, the FDA recently approved the oral suspension in children 6 months of age and older, but it is not yet available.[197]

Aprepitant and fosaprepitant (Emend) as well as rolapitant (Varubi) have not been studied in patients less than 18 years old. Neither dronabinol (Marinol) nor nabilone (Cesamet) have been studied in children. Caution is recommended in prescribing dronabinol or nabilone for children because of the psychoactive effects.

The safety and effectiveness of netupitant/palonosetron (Akynzeo) in pediatric patients has not been established.

Safety and effectiveness of oral metoclopramide (Reglan, Metozolv ODT) in pediatric patients have not been established. Metoclopramide injectable (Reglan) is used in pediatric patients to facilitate small bowel intubation.

Trimethobenzamide (Tigan) injection is contraindicated in pediatric patients.

Dimenhydrinate (Dramamine OTC), and diphenhydramine (Benadryl) have been used to prevent and treat N/V associated with motion sickness in pediatric populations. Use of meclizine (Antivert, Bonine, Univert) in children less than 12 years of age is not recommended. The safety and efficacy of doxylamine/pyridoxine (Diclegis) has not been established in pediatric patients.

Promethazine (Phenergan) and prochlorperazine (Compro) should not be used in pediatric patients less than 2 years of age. Safety and effectiveness of scopolamine (Transderm-Scop) in children have not been established.

In pediatrics receiving HEC or MEC, ASCO recommends treatment with a 5-HT_3 receptor antagonist and corticosteroids, noting that higher weight-based dosing may be necessary.[198,199]

Pregnancy

Doxylamine/pyridoxine (Diclegis) is pregnancy category A and is intended for use in pregnant women.

The NK-1 receptor antagonist, aprepitant (Emend), is Pregnancy Category B. The 5-HT_3 antagonists, ondansetron (Zofran, Zuplenz), granisetron, dolasetron (Anzemet), and palonosetron (Aloxi) are Pregnancy Category B. Metoclopramide (Reglan, Metozolv ODT) is Pregnancy Category B.

Netupitant/palonosetron (Akynzeo) is Pregnancy Category C. The cannabinoids, dronabinol (Marinol) and nabilone (Cesamet), are Pregnancy Category C. Trimethobenzamide (Tigan), promethazine (Phenergan), prochlorperazine (Compro), and scopolamine (Transderm-Scop) are Pregnancy Category C.

There are no data available on the use of rolapitant (Varubi) in pregnant women to discern drug-associated risks. There were no teratogenic or embryo-fetal effects observed with rolapitant in animal reproduction studies.

Geriatrics

Dronabinol (Marinol) and nabinol (Cesamet) should be used with caution in elderly patients because they may be more sensitive to its neurological, psychoactive, and postural hypotensive effects. Dose selection should be initiated at the low end of the dosing range. Patients with dementia are at an increased risk for falls due to the underlying disease state and should be monitored closely and placed on falls precautions prior to initiation of therapy.

Dolasetron (Anzemet) injectable is contraindicated in geriatric patients for prevention of N/V associated with initial and repeat courses of emetogenic cancer chemotherapy.

DOSAGES[200,201,202,203,204,205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222]

Antiemetic Drug	Prevention of chemotherapy-induced N/V		Prevention of radiotherapy-induced N/V in adults or Other Use	Prevention of post-operative N/V		Availability
	Adult	Pediatric		Adult	Pediatric	
NK_1 receptor antagonists						
aprepitant (Emend)	125 mg 1 hour prior to chemotherapy day 1, then 80 mg once daily in the morning on days 2 and 3 as part of regimen including corticosteroid and a 5-HT_3 antagonist (dosing is the same for adults and pediatric patients > 30 kg)	--	--	40 mg within 3 hours prior to induction of anesthesia	--	capsules: 40, 80, 125 mg bi-pack: two 80 mg capsules tri-fold/tripack pack: one 125 mg capsule and two 80 mg capsules
fosaprepitant dimeglumine (Emend)	Single Dose regimen for Highly Emetogenic Chemotherapy (HEC): 150 mg on day 1 as an infusion over 20 to 30 minutes approximately 30 minutes prior to chemotherapy in combination with a corticosteroid and a 5-HT_3 antagonist Three day dosing regimen for HEC and moderately emetogenic chemotherapy [MEC]: 115 mg on day 1 as an infusion over 15 minutes approximately 30 minutes prior to chemotherapy in combination with a corticosteroid and a 5-HT_3 antagonist; oral Emend 80 mg capsules are administered daily on days 2 and 3	--	--	--	--	injection: 150 mg per vial

Dosages (continued)

Antiemetic Drug	Prevention of chemotherapy-induced N/V		Prevention of radiotherapy-induced N/V in adults or Other Use	Prevention of post-operative N/V		Availability
	Adult	Pediatric		Adult	Pediatric	
NK_1 receptor antagonists (continued)						
rolapitant (Varubi)	Administer prior to the initiation of each cycle of chemotherapy without regard to food, but at no less than 2 week intervals; Rolapitant is to be used in combination with a 5-HT_3 receptor antagonist and dexamethasone HEC:180 mg (2 tablets) administered 1 to 2 hours prior to chemotherapy on day 1 with a corticosteroid and a 5-HT_3 antagonist (corticosteroid also administered days 2-4) MEC: 180 mg (2 tablets) administered 1 to 2 hours prior to chemotherapy on day 1 with a corticosteroid and a 5-HT_3 antagonist (5-HT_3 antagonist administered per prescribing information)	--	--	--	--	tablets: 90 mg

Dosages (continued)

Antiemetic Drug	Prevention of chemotherapy-induced N/V		Prevention of radiotherapy-induced N/V in adults or Other Use	Prevention of post-operative N/V		Availability
	Adult	Pediatric		Adult	Pediatric	
5-HT$_3$ antagonists						
dolasetron (Anzemet)	100 mg orally within 1 hour before chemotherapy	2 to 16 years: 1.8 mg/kg (up to 100 mg) orally within 1 hour before chemotherapy Anzemet injection solution may be mixed into apple or apple-grape juice for oral dosing in pediatric patients	--	100 mg orally within 2 hours before surgery 12.5 mg IV given 15 minutes before the cessation of anesthesia (prevention) or as soon as N/V presents (treatment)	2 to 16 years: 1.2 mg/kg orally (up to 100 mg) given within 2 hours before surgery 2 to 16 years: 0.35 mg/kg IV (up to 12.5 mg IV) given 15 minutes before the cessation of anesthesia or as soon as N/V presents Anzemet injection solution may be mixed into apple or apple-grape juice for oral dosing in pediatric patients; The recommended oral dose for ages 2 to 16 years old is 1.2 mg/kg up to 100 mg within 2 hours before surgery	tablets: 50, 100 mg injection: 12.5 mg per 0.625 mL 100 mg per 5 mL 500 mg per 25 mL

Dosages (continued)

Antiemetic Drug	Prevention of chemotherapy-induced N/V		Prevention of radiotherapy-induced N/V in adults or Other Use	Prevention of post-operative N/V		Availability
	Adult	Pediatric		Adult	Pediatric	
5-HT$_3$ antagonists (continued)						
granisetron	Oral: 2 mg up to 1 hour before chemotherapy for 1 dose OR 1 mg up to 1 hour before chemotherapy followed by 1 mg 12 hours after the first dose Injectable: 10 mcg/kg IV given up to 30 minutes before initiation of chemotherapy only on the day(s) chemotherapy is given	Injectable (2 to 16 years): 10 mcg/kg	2 mg once daily taken within 1 hour of radiation	Injectable: Prevention: 1 mg IV over 30 seconds before induction or immediately before reversal of anesthesia. Treatment: 1 mg IV over 30 seconds	--	tablets: 1 mg injection: 0.1 mg per mL, 1 mg per mL (single use vials), 4mg/4mL (multi-use vials)
granisetron transdermal (Sancuso)	Apply single patch to upper outer arm 24 hours prior to chemotherapy; remove 24 hours after completion of chemotherapy The patch can be worn for up to 7 days	--	--	--	--	transdermal patch containing 34.3 mg granisetron that releases 3.1 mg over 24 hours for 7 days

Dosages (continued)

Antiemetic Drug	Prevention of chemotherapy-induced N/V		Prevention of radiotherapy-induced N/V in adults or Other Use	Prevention of post-operative N/V		Availability
	Adult	Pediatric		Adult	Pediatric	
5-HT$_3$ antagonists (continued)						
ondansetron (Zofran, Zuplenz)	HEC: 24 mg (three -8 mg tabs) given 30 minutes before start of chemotherapy; MEC: 8 mg given 30 minutes before start of chemotherapy with a subsequent dose 8hours after the first dose; 8 mg should then be given every 12 hours for 1 to 2 days following completion of chemotherapy Injection: 0.15 mg/kg IV for 3 doses up to a maximum of 16 mg per dose The first dose is infused over 15 minutes starting 30 minutes before the start of chemotherapy; subsequent doses (0.15 mg/kg up to 16 mg per dose) are administered 4 and 8 hours after the first dose	HEC: No experience with 24 mg dosage MEC: 4-11 years: 4 mg given 30 minutes before chemotherapy with subsequent doses 4 and 8 hours after the first dose; 4 mg should be given every 8 hours for 1 to 2 days after completion of chemotherapy ≥ 12 years: same as adult. Injection: 6 months – 18 years: 0.15 mg/kg IV for 3 doses up to a maximum of 16 mg per dose; the first dose is given 30 minutes prior to moderately to HEC Subsequent doses (0.15 mg/kg IV up to a maximum of 16 mg per dose) are administered 4 and 8 hours after the first dose;(infused over 15 minutes)	8 mg up to 2 hours before radiation and up to 3 times daily for 1 to 2 days	16 mg (two-8mg tabs) 1 hour before induction of anesthesia 4 mg IV over 2 to 5 minutes, immediately before induction of anesthesia or postoperatively if the patient did not receive prophylactic antiemetics and has N/V within 2 hours after surgery	1 month to 12 years: <40 kg: 0.1 mg/kg IV over 2 to 5 minutes > 40 kg: 4 mg IV over 2 to 5 minutes immediately prior to or following anesthesia induction or post-operatively if the patient did not receive prophylactic antiemetics and has N/V shortly after surgery	tablets: 4, 8, 24 mg oral soluble film (Zuplenz): 4, 8 mg oral solution: 4 mg/5 mL tablets, orally disintegrating (ODT): 4, 8 mg injection: 2 mg per mL solution for injection: 32 mg/50 mL in 5% dextrose, 32 mg/50 mL in 0.9% sodium chloride

Dosages (continued)

Antiemetic Drug	Prevention of chemotherapy-induced N/V		Prevention of radiotherapy-induced N/V in adults or Other Use	Prevention of post-operative N/V		Availability
	Adult	Pediatric		Adult	Pediatric	
5-HT$_3$ antagonists (continued)						
palonosetron (Aloxi)	A single 0.25 mg IV dose administered over 30 seconds Dosing should occur approximately 30 minutes prior to start of chemotherapy	--	--	A single 0.075 mg IV dose administered over 10 seconds immediately prior to the induction of anesthesia	--	injection (single use vial): 0.25 mg per 5 mL
Combination products						
netupitant/ palonosetron (Akynzeo)	One 300/0.5 mg capsule administered approximately 1 hour prior to the start of chemotherapy as part of a regimen including dexamethasone	--	--	--	--	capsules: 300 mg netupitant/0.5 mg palonosetron
Cannabinoids						
dronabinol (Marinol)	Initial dose of 5 mg/m^2 given 1 to 3 hours prior to chemotherapy, then every 2 to 4 hours after chemotherapy for a total of 4 to 6 doses per day; the initial starting dose may be adjusted in increments of 2.5 mg/m^2 if necessary up to a maximum of 15 mg/m^2 (per dose)	--	--	--	--	capsules: 2.5, 5, 10 mg

Dosages (continued)

Antiemetic Drug	Prevention of chemotherapy-induced N/V		Prevention of radiotherapy-induced N/V in adults or Other Use	Prevention of post-operative N/V		Availability
	Adult	Pediatric		Adult	Pediatric	
Cannabinoids (continued)						
nabilone (Cesamet)	Usual adult dose is 1 to 2 mg twice daily; 1 or 2 mg may be given the night prior to chemotherapy or 1 to 3 hours before initial chemotherapy; maximum daily dose of 6 mg in divided doses (3 times a day); the medication may be administered 2 or 3 times a day during the entire course of each chemotherapy cycle and for 48 hours after the last dose of each chemotherapy cycle	--	--	--	--	capsules: 1 mg

Dosages (continued)

Antiemetic Drug	Prevention of chemotherapy-induced N/V		Prevention of radiotherapy-induced N/V in adults or Other Use	Prevention of post-operative N/V		Availability
	Adult	Pediatric		Adult	Pediatric	
Antidopaminergic Agents						
metoclopramide (Metozolv ODT, Reglan)	1 to 2 mg/kg IV 30 minutes before chemotherapy and repeated every 2 hours for 2 doses, then every 3 hours for 3 doses	--	Relief of symptomatic GERD: 10 to 15 mg orally up to 4 times daily at least 30 minutes prior to eating and at bedtime for up to 12 weeks Relief of symptoms associated with diabetic gastroparesis: 10 mg IV, IM or orally 4 times daily at least 30 minutes prior to eating and at bedtime for 2 to 8 weeks; therapy should not exceed 12 weeks Facilitation of intestinal intubation or as a diagnostic aid in gastrointestinal radiography- 10 mg IV in a single dose	10-20 mg IM or IV near the end of surgery. Repeat every 4 to 6 hours as necessary; if required, a 20 mg dose may be used	--	tablets: 5, 10 mg orally disintegrating tablets: 5, 10 mg solution: 5 mg/5 mL injection: 5 mg per mL

Dosages (continued)

Antiemetic Drug	Prevention of chemotherapy-induced N/V		Prevention of radiotherapy-induced N/V in adults or Other Use	Prevention of post-operative N/V		Availability
	Adult	Pediatric		Adult	Pediatric	
Antihistamines						
doxylamine/ pyridoxine (Diclegis)	--	--	Nausea and vomiting of pregnancy : initially, take 2 tablets orally at bedtime; if symptoms persist, take an additional tablet in the morning on Day 3; if symptoms persist, take an additional tablet mid afternoon on Day 4 (Max dose 4 tablets per day)	--	--	delayed release tablets: 10 mg doxylamine/ 10 mg pyridoxine
Others						
phosphorated carbohydrate solution (Emetrol OTC)	--	--	Relief of upset stomach associated with nausea: ages 2 to < 12 years: 1-2 teaspoons age > 12 years: 1-2 tablespoons May repeat dose every 15 minutes or until distress subsides; should not be taken for more than 1 hour (5 doses)	--	--	3.74 g total sugar + 21.5 mg phosphoric acid per 5 mL
trimethobenzamide (Tigan)	--	--	Nausea and vomiting - 250 or 300 mg capsule: 3 to 4 times daily or 200mg IM 3 to 4 times daily The suppository formulation has not been proven effective for nausea and vomiting	--	--	injection: 100 mg per mL capsules: 300 mg suppository: 200 mg

Dosages (continued)

Antivertigo Agents	Adult	Pediatric	Availability
Antihistamines			
dimenhydrinate (Dramamine OTC, Motion Sickness OTC)	▪ Adults and children 12 years and older: Oral: 1 to 2 tablets every 4 to 6 hours (do not exceed 8 tablets in 24 hours) ▪ Injection: 50 to 100 mg IM or IV every 4 hours (do not exceed 300 mg in 24 hours)	Children ages 6 to 12 years: ▪ Oral: ½ to 1 tablet every 6 to 8 hours (do not exceed 3 tablets in 24 hours) ▪ Oral: Children ages 2 to 6 years: ¼ to ½ tablet every 6 to 8 hours (do not exceed more than 1.5 tablets in 24 hours) ▪ Injection: Children ages 2 to 12 years: 1.25 mg/kg or 37.5 mg/m^2 BSA IM or IV every 6 hours (do not exceed 300 mg in 24 hours)	tablets: 50 mg chewable tablets: 25, 50 mg injection: 50 mg per mL
diphenhydramine (Benadryl)	▪ Injection: 10 mg IV or IM initially then 20 to 50 mg every 2 to 3 hours as needed (do not exceed 400mg in 24 hours) ▪ Oral: 25 to 50 mg every 4 to 6 hours in adults and children ages 12 years and older (do not to exceed 300 mg in 24 hours)	▪ Injection: Ages 6 to 12 years: 1 to 1.5 mg per kg IV or IM every 6 hours, not to exceed 300 mg per day ▪ Oral: Ages 6 to 12 years: 12.5 mg to 25 mg every 4 to 6 hours (do not exceed 150 mg in 24 hours) ▪ Oral and Injection: ages less than 6 years: safety and efficacy have not been established	tablets: 25, 50 mg capsules: 25, 50 mg chewable tablet: 25 mg injection: 50 mg per mL oral dissolving film: 12.5, 25 mg oral dissolving tablet: 12.5, 25 mg oral solution: 12.5 mg per 5 mL, 50 mg per 30 mL
meclizine (Antivert, Dramamine Less Drowsy OTC, Bonine, Univert)	▪ Motion Sickness: adults and children 12 years and older (OTC Dramamine Less Drowsy): 25 to 50 mg taken 1 hour prior to travel; may repeat dose every 24 hours as needed ▪ Vertigo: Adults and children 12 years and older: 25 to 100 mg daily in divided doses	--	chewable tablets: 25 mg tablets: 12.5, 25 mg

Dosages (continued)

Antivertigo Agents	Adult	Pediatric	Availability
Phenothiazines			
prochlorperazine (Compro)	Immediate release tablets: 5 to 10 mg 3 to 4 times daily Sustained release capsules: 10 or 15 mg every 12 hours Rectal suppositories: 25 mg twice daily IV or IM: 5 to 10 mg repeated every 3 to 4 hours as needed (max dose is 40 mg/day)	Oral or rectal: Children 2 to 12 years (weight 18 to 39 kg): 2.5 mg 3 times per day or 5 mg twice per day (max: 15 mg/day) Children 2 to 12 years (weight 14 to 17 kg): 2.5 mg 2 to 3 times per day (max: 10 mg/day) Children 2 to 12 years (weight 9 to 13 kg): 2.5 mg once or twice per day (max: 7.5 mg/day) Children < 2 years of age and infants (weight < 9 kg): Dosage not established IV or IM: Children 2 to 12 years (weight 18 to 39 kg): 0.132 mg per kg deep IM injection given 3 to 4 times per day, not to exceed 10 mg per day on the first day of treatment (max: 15 mg per day on subsequent days) Children 2 to 12 years (weight 14 to 17 kg): 0.132 mg per kg deep IM injection given 3 to 4 times per day (max: 10 mg per day) Children 2 to 12 years (weight 9 to 13 kg): 0.132 mg per kg deep IM injection given 3 to 4 times per day (max: 7.5 mg per day) Children < 2 years and infants (weight < 9 kg): Dosage not established	tablets, immediate-release: 5, 10 mg suppositories: 25 mg injection: 5 mg per mL
promethazine (Phenergan)	Motion Sickness: Adults: 25 mg (oral or rectal) 30 to 60 minutes prior to departure, then every 12 hours as needed N/V: Adults: 12.5 to 25 (oral, rectal, IV, IM) mg every 4 to 6 hours as needed	Motion Sickness: Children over 2 years of age: 12.5 to 25 mg (oral or rectal) twice daily as needed with first dose given 30 to 60 minutes prior to departure N/V: Children over 2 years of age: 0.5 mg per pound (oral or rectal), max 25 mg per dose, every 4 to 6 hours as needed Children over 2 years of age: 6.25 to 12.5 mg (IM or IV) every 4 to 6 hours as needed (max: 25mg/dose)	tablets: 12.5, 25, 50 mg oral solution: 6.25 mg per 5 mL suppositories: 12.5, 25, 50 mg injection: 25 mg per mL, 50 mg per mL

Dosages (continued)

Antivertigo Agents	Adult	Pediatric	Availability
Anticholinergics			
scopolamine (Transderm-Scop)	N/V: SC injection: 0.6 to 1 mg Motion sickness: Transdermal: 1 disc applied behind the ear 4 hours prior to antiemetic need; disc may stay in place for up to 3 days (If repeat dose needed, apply to skin behind opposite ear) Oral: 250 to 800 mcg 1 hour prior to need for antiemetic	N/V: SC injection: 0.006 mg per kg	injection: 0.4 mg per mL transdermal: 1.5 mg per 72 hours (delivers 1 mg over 72 hours)

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

A number of clinical trials have evaluated ondansetron compared to other antiemetic agents. None of these trials have involved the use of the oral film used as the delivery mechanism in Zuplenz. While no clinical trials have been undertaken to evaluate Zuplenz, this product has demonstrated bioavailability similar to that of the orally disintegrating dosage form of ondansetron.

Antivertigo agents used in the prevention and treatment of N/V associated with motion sickness are included in this review. There is a paucity of clinical trial data available related to motion sickness, and the primary treatment option for this condition involves the use of older medications including the more sedating antihistamines. No clinical trials are included at this time related to vertigo and motion sickness prophylaxis and treatment.

aprepitant (Emend) plus standard of care versus placebo plus standard of care

Patients receiving cisplatin were blindly assigned to receive 1 of the following 3 regimens: (1) aprepitant 375 mg 1 hour before cisplatin on day 1 and aprepitant 250 mg on days 2 through 5 (n=35); (2) aprepitant 125 mg before cisplatin and aprepitant 80 mg on days 2 through 5 (n=81); or (3) placebo before cisplatin on days 2 through 5 (n=86).[223] All groups received ondansetron 32 mg and dexamethasone 20 mg before cisplatin, and dexamethasone 8 mg on days 2 through 5. The primary endpoint was complete response (no emesis and no rescue therapy) over 5 days following cisplatin in up to 6 cycles. The aprepitant 375/250 mg regimen was discontinued early in light of new pharmacokinetic data. In the first cycle, 64% of patients in the aprepitant group and 49% in the standard therapy group had a complete response ($p<0.05$). Thereafter, complete response rates for the aprepitant group were still 59% by cycle 6, but decreased to 34% by cycle 6 for the standard therapy group ($p<0.05$).

A randomized, double-blind, placebo controlled, cross over designed trial was conducted to compare aprepitant versus a placebo.[224] Patients were randomized to receive aprepitant 125 mg on day 3 and 80 mg once per day on days 4 through 7 or placebo in addition to a commercially available $5HT_3$ receptor antagonist on days 1 through 5 and dexamethasone on days 1 and 2. The cross over design allowed patients to serve as their own control. The primary endpoint of the study was complete response (CR) defined as no emetic episodes with no use of rescue medication, of acute (days 1

through 5), and delayed (days 6 through 8) chemotherapy-induced nausea and vomiting (CINV). Secondary endpoints included emetic episodes, use of rescue medication, nausea measurement based on a visual analogue scale (VAS), and patient stated preference after second cycle. Seventy-one patients 15 years of age and older with germ cell tumors receiving a standard 5 day cisplatin regimen were enrolled. Of these patients, 60 completed the study and were available for analysis. Twenty-five (42%) of the patients achieved CR with aprepitant while 8 (13%) achieved CR in the placebo group ($p<0.001$) during days 1 through 8. Of the 25 patients that received CR with aprepitant, 7 received CR when they crossed over to the placebo arm and of the 8 patients that received CR on placebo, 7 received CR when they crossed over to aprepitant. Twenty-eight (47%) of the patients in the aprepitant group achieved a CR in the acute phase compared with 9 (15%) in the placebo group ($p<0.001$). Thirty-eight patients (63%) in the aprepitant group achieved a CR in the delayed phase compared to 21 (42%) of the patients in the placebo group ($p<0.001$).

aprepitant (Emend) versus ondansetron (Zofran)

Patients scheduled to undergo craniotomy under general anesthesia were enrolled in this prospective, double-blind, randomized study.[225] Patients were randomized to receive oral aprepitant 40 mg (or matching placebo) 1 to 3 hours before induction of anesthesia or ondansetron 4 mg IV (or placebo) within 30 minutes of the end of surgery. All patients received dexamethasone 10 mg after induction of anesthesia. One hundred four patients completed the study. The cumulative incidence of vomiting at 48 hours was 16% in the aprepitant group and 38% in the ondansetron group ($p=0.0149$). The incidence of vomiting was also decreased in the aprepitant group at 2 hours (6% versus 21%, $p=0.0419$) and 24 hours (14% versus 36%, $p=0.0124$). From 0 to 48 hours, there was no difference between the aprepitant and ondansetron groups in the incidence of nausea (69% versus 60%), nausea scores, need for rescue antiemetics (65% versus 60%), complete response (no post-operative nausea and vomiting [PONV] and no rescue, 22% versus 36%), or patient satisfaction with the management of PONV. Aprepitant/dexamethasone was more effective than ondansetron/dexamethasone for prophylaxis against post-operative vomiting in adult patients undergoing craniotomy under general anesthesia. However, there was no difference between the groups in the incidence or severity of nausea, need for rescue antiemetics, or in complete response between the groups.

aprepitant (Emend) plus ondansetron (Zofran) versus placebo plus ondansetron (Zofran)

A prospective, randomized, double-blind study was performed to assess the occurrence of post-operative nausea and vomiting and severity of nausea for up to 48 hours in 150 adult patients undergoing plastic surgery.[226] Patients were randomized to take 40 mg of oral aprepitant plus 4 mg intravenous ondansetron (Group A, n=75) or oral placebo plus 4 mg intravenous ondansetron (Group B, n=75). Oral aprepitant or placebo was given to patients 2 hours prior to their scheduled operation. All patients in both groups received the same anesthetic regimen and 4 mg of intravenous ondansetron during surgery. All patients from both groups were allowed any of the institution's formulary anti-emetics and/or pain medications post-operatively. A blinded investigator recorded the occurrence of nausea and vomiting before surgery, on admission to the post-anesthesia unit, and hourly until the patient was discharged using a verbal rating scale. Retching and vomiting were evaluated as a 'yes' or 'no'. After discharge, patients rated their nausea, vomiting, and retching using the same scale and logged which analgesics they used. No patients experienced vomiting before being admitted to the post-anesthesia care unit. All episodes of vomiting occurred in the first 12 hours after being admitted

to the post-anesthesia care unit. Patients in Group A (9.3%) experienced less vomiting than those in Group B (29.7%, p=0.003), indicating a relative risk reduction of 31.3%. Using a Kaplan-Meier plot the hazards of vomiting 12 hours post-surgery indicated an increase incidence of vomiting in Group B (p=0.006). No patient in Group A or B experienced vomiting 12 hours after being admitted to the post-anesthesia care unit. The reported mean nausea scores for Group A were lower than Group B, 5 and 8, respectively (p=0.014). The severity of nausea was higher in Group B (p=0.24). There were no significant differences in anti-emetic usage (42.7% in Group A and 44.6% in Group B) or complete response (absence of vomiting and no need of rescue anti-emetic medications) between Group A and Group B (26 patients and 20 patients, respectively, p=0.288). The study concluded aprepitant decreases post-operative nausea and vomiting and is useful when used in combination with other antiemetics for post-operative nausea and vomiting.

aprepitant (Emend) versus dexamethasone

A randomized, double-blind, multicenter study was performed in 580 chemotherapy-naive patients with breast cancer treated with anthracyclines plus cyclophosphamide to assess the efficacy of aprepitant and dexamethasone in delayed CINV.[227] Before chemotherapy, all patients were treated with IV palonosetron 0.25 mg, dexamethasone 8 mg, and oral aprepitant 125 mg. On days 2 and 3, patients randomly received oral dexamethasone 4 mg twice per day or aprepitant 80 mg once per day. The primary end point was rate of complete response (no vomiting or rescue treatment) from days 2 to 5 after chemotherapy. Both day 1 (87.6% for dexamethasone and 84.9% for aprepitant [p<0.39]) and days 2 through 5 (79.5% for dexamethasone and 79.5% for aprepitant [p<1]) complete response rates were similar and did not reach statistical significance.

rolapitant (Varubi), dexamethasone, and granisetron versus placebo, dexamethasone, and granisetron

Two randomized, double-blind, parallel group studies (Study 1 and Study 2) compared a rolapitant regimen (rolapitant, dexamethasone, and the 5-HT_3 receptor antagonist, granisetron) with control therapy (placebo, dexamethasone, granisetron) in patients receiving chemotherapy including cisplatin > 60 mg/m^2 (highly emetogenic chemotherapy [HEC]).[228] The primary endpoint in both studies was complete response (no emetic episodes and no rescue medication) in the delayed phase (25 to 120 hours) of CINV. In Study 1, a total of 532 patients were randomized to either the rolapitant or control regimens. Patients ranged from 20 to 90 years of age, with a mean age of 57 years. The mean cisplatin dose was 77 mg/m^2. Eighty-two percent of patients received a concomitant chemotherapy agent in addition to cisplatin with the most common agents being gemcitabine (17%), paclitaxel (12%), fluorouracil (11%) and etoposide (10%). In Study 2, a total of 555 patients were randomized to either the rolapitant or control regimens. Patients ranged from 18 to 83 years of age, with a mean age of 58 years. The mean cisplatin dose was 76 mg/m^2. Eighty-five percent of patients received a concomitant chemotherapy agent in addition to cisplatin with the most common agents being vinorelbine (16%), gemcitabine (15%), fluorouracil (12%) and etoposide (11%). In both studies, a significantly greater proportion of patients in the rolapitant group had complete responses in the delayed phase of nausea and vomiting as compared to patients in the control group (Study 1: 73% versus 58%; Study 2: 70% versus 62%; p<0.001 for both).

A randomized, double-blind, parallel group study compared a rolapitant regimen (rolapitant 180 mg on day 1, dexamethasone, and the 5-HT_3 receptor antagonist granisetron) to control therapy (dexamethasone and granisetron) in patients receiving a moderately emetogenic chemotherapy (MEC)

regimen that included at least 50% of patients receiving a combination of anthracycline and cyclophosphamide.229 The primary endpoint was complete response (no emetic episodes and no rescue medication) in the delayed phase (25 to 120 hours) of chemotherapy-induced nausea and vomiting. A total of 1,369 patients were randomized to rolapitant regimen or control therapy. Patients ranged from 22 to 88 years of age, with a mean age of 57 years. A significantly greater proportion of patients receiving rolapitant had completed responses in the delayed phase of nausea and vomiting than patients in the control group (71% versus 62%; p=0.0002).

dolasetron (Anzemet) versus ondansetron (Zofran)

A multicenter, randomized, double-blind study was designed to compare the antiemetic efficacy and safety of single oral doses of dolasetron with a multiple-dose regimen of oral ondansetron in 399 cancer patients receiving MEC.[230] Single oral doses of 25, 50, 100, or 200 mg of dolasetron were administered 1 hour prior to the initiation of chemotherapy. Ondansetron 8 mg, or matching placebo for patients randomized to dolasetron, was given 1.5 hours before and 6.5, 14.5, and 22.5 hours after the start of chemotherapy. A statistically significant ($p<0.001$) linear dose-response relationship was observed over the entire dolasetron dosage range for all efficacy parameters. Complete response rates were 45%, 49.4%, 60.5%, and 76.3% for 25, 50, 100, and 200 mg dolasetron, respectively, and 72.3% for ondansetron patients. Overall, there were no significant differences in the incidence of adverse events between any of the dolasetron doses, or between dolasetron and ondansetron; headache was most frequently reported (approximately 15% for each drug). In the study, a single oral 200 mg dolasetron dose was therapeutically equivalent to multiple-dose ondansetron in the prevention of N/V following MEC.

granisetron versus ondansetron (Zofran)

A double-blind study was conducted to determine the efficacy of oral ondansetron, oral granisetron, and IV ondansetron for the prevention/control of N/V associated with high-dose chemotherapy or radiotherapy prior to hematopoietic stem cell transplantation.[231] In addition to dexamethasone 10 mg IV, 102 patients were randomized to receive either ondansetron 8 mg orally every 8 hours, granisetron 1 mg orally every 12 hours, or ondansetron 32 mg IV every 24 hours, each given on days 1 and 2. Overall complete response rates were 48% for oral ondansetron, 47% for oral granisetron, and 49% for IV ondansetron; this difference is not statistically significant (p=NS). Overall major efficacy rates were 82% for oral ondansetron, 84% for oral granisetron, and 81% for IV ondansetron (p=NS). Mean VAS nausea scores were 32 for oral ondansetron, 32 for oral granisetron, and 27 for IV ondansetron (p=NS).

A double-blind, randomized, crossover study comparing granisetron 3 mg/day and ondansetron 24 mg/day enrolled 309 patients receiving 2 cycles of identical chemotherapy over 5 days.[232] Primary efficacy variables were prospectively defined as complete response (no vomiting and mild or absent nausea) over 5 days and patient preference. Both agents achieved good control of emetic symptoms with five-day complete response rates of 44% on granisetron and 39.8% on ondansetron (p=NS). Complete response rates were very similar in patients receiving either cisplatin or ifosfamide. There was a statistically significant difference in patient preference in favor of granisetron (p=0.048).

A randomized, cross-over pilot study of post-operative nausea and vomiting (PONV) was conducted in 250 female patients who received prophylactic ondansetron 4 mg at the end of a surgical procedure requiring general anesthesia.[233] Women were then followed post-operatively for 4 hours. Eighty-eight of the women developed PONV and were randomly assigned to receive 1 of the following: a repeat

dose of ondansetron 4 mg (n=30), granisetron 1 mg (n=30), or granisetron 0.1 mg (n=28). They were followed for 24 hours. Patients who received the repeat dose of ondansetron had a complete response of 57%, those receiving granisetron 1 mg or 0.1 mg had complete responses of 60% and 68%, respectively. This difference was not statistically significant (p=0.773).

The efficacy of oral granisetron and oral ondansetron was compared for preemptive antiemesis in women undergoing modified radical mastectomy.[234] A randomized, double-blind, controlled study assigned 90 women, aged 18 to 65 years old, scheduled to receive radical mastectomies to receive oral granisetron 2 mg, ondansetron 4 mg, or placebo (30 women in each group) 1 hour before induction of anesthesia. Post-operative N/V was assessed until 24 hours post surgery. A complete response in 0 to 2 hours after anesthesia was found in 43%, 63%, and 90% of patients who had received placebo, granisetron, or ondansetron, respectively; of these, the percentages of patients requiring rescue antiemetics were 40%, 17%, and 7%. The presence of N/V was less than 23% after 2 hours in all 3 groups. In addition, after 2 hours, N/V scores and need for antiemetics were similar in all 3 groups. Oral ondansetron 4 mg provided better preemptive antiemesis than oral granisetron 2 mg and placebo in the 2 hours following surgery with general anesthesia.

granisetron versus granisetron transdermal (Sancuso)

A phase 3, randomized, parallel-group, double-dummy, double-blind trial was conducted in 641 patients who received multi-day chemotherapy to compare the efficacy, tolerability, and safety of granisetron transdermal to oral granisetron 2 mg once daily in the prevention of N/V.[235] The primary endpoint was proportion of patients achieving no vomiting and/or retching, no more than mild nausea, and without use of a rescue medication from the first administration until 24 hours after start of the last day's administration of multi-day chemotherapy. The effect of granisetron transdermal was established in 60.2% of patients and in 64.8% of the patients taking granisetron orally (p=NS).

palonosetron (Aloxi) versus granisetron versus palonosetron plus aprepitant (Emend) versus palonosetron plus dexamethasone

A randomized, double-blind, placebo controlled study was conducted in 1,021 patients to determine the comparative efficacy of four treatment regimens.[236] Patients at least 18 years of age with a cancer diagnosis scheduled to receive their first treatment with any dose or schedule other than multiple day doses of doxorubicin, epirubicin, cisplatin, carboplatin, or oxaliplatin were included (both high and moderate emetogenic potential). Patients were assigned to either palonosetron 0.25 mg IV plus dexamethasone 20 mg IV plus oral placebo on day 1 with oral prochlorperazine on days 2 and 3 (group 1), granisetron 1 mg IV plus dexamethasone 20 mg IV plus oral placebo day 1 with oral prochlorperazine on days 2 and 3 (group 2), palonosetron 0.25 mg IV plus dexamethasone 12 mg IV plus aprepitant 125 mg orally on day 1 with aprepitant 80 mg orally and dexamethasone 8 mg orally on days 2 and 3 (group 3), and palonosetron 0.25 mg IV plus dexamethasone 20 mg IV plus placebo orally on day 1 with prochlorperazine 10 mg orally and dexamethasone 8 mg orally on days 2 and 3 (group 4). The primary outcome of the study was to determine efficacy through a difference in mean delayed nausea in the following scenarios: palonosetron in comparison to granisetron, palonosetron with or without an additional dose of dexamethasone on day 2 in addition to prochlorperazine, and aprepitant in comparison to prochlorperazine with or without dexamethasone on day 2. Nausea was reported on a home record at 4 time intervals per day (morning, afternoon, evening, and night) and was rated using a 7 point scale. Of the 1,021 patients that were randomly assigned to a group, 944 patients had evaluable data for delayed nausea (DN). In the group 1 to group 2 comparison, palonosetron was not

statistically significantly more effective than granisetron with a mean DN difference of -0.013 (95% CI, -0.225 to 0.2; p=0.718). In the group 1 to group 4 comparison, the addition of dexamethasone on days 2 and 3 resulted in a more effective treatment with a mean DN difference of 0.195 (95% CI, -0.017 to 0.407; p=0.01). In the group 3 to group 4 comparison, aprepitant was not statistically significantly more effective than prochlorperazine in combination with palonosetron and dexamethasone with a mean DN difference of -0.025 (95% CI, -0.236 to 0.186; p=0.557).

palonosetron (Aloxi) versus ondansetron, dolasetron, and granisetron

Four randomized, double-blind, phase 3 trials compared palonosetron with ondansetron, dolasetron, and granisetron and results were reported as a pooled analysis of patient level data.[237] Two of the trials were conducted in patients scheduled to receive MEC and 2 in patients scheduled to receive HEC. Dosages included in the studies analyzed were palonosetron 0.25 mg or 0.75 mg, ondansetron 32 mg, dolasetron 100 mg, and granisetron 40 μg/kg. Endpoints included complete response (no emesis and no rescue antiemetics) in the acute, delayed, and overall post chemotherapy periods, and secondary outcomes of complete control (no emesis, no rescue antiemetics, and no more than mild nausea), number of emetic episodes, and nausea severity. Complete response rates were significantly higher for palonosetron (n=1,787) versus older 5-HT_3 antagonists (ondansetron, dolasetron, and granisetron) (n=1,175) in the delayed (57% versus 45%; p<0.0001) and overall periods (51% versus 40%; p< 0.0001) but not the acute phase (69% versus 66%; p=0.091). Significant differences in secondary outcomes complete control rates and nausea severity were observed for the delayed and overall periods and in emetic episodes for all 3 periods. The incidence of treatment-related adverse events was similar with palonosetron (0.25 mg, 20%; 0.75 mg, 26.5%) and older 5-HT_3 antagonists (27.5%).

dronabinol (Marinol), ondansetron (Zofran), combination therapy versus placebo

A 5-day, double-blind, placebo-controlled study was conducted in 64 patients to compare the efficacy and tolerability of dronabinol, ondansetron, or the combination for delayed CINV.[238] Patients receiving moderately to highly emetogenic chemotherapy received dexamethasone 20 mg orally, ondansetron 16 mg IV, and either placebo or dronabinol 2.5 mg pre-chemotherapy on day 1. Patients randomized to active treatment (dronabinol and/or ondansetron) also received dronabinol 2.5 mg after chemotherapy on day 1. On day 2, fixed doses of placebo, dronabinol 10 mg, ondansetron 16 mg, or combination therapy were administered. On days 3 to 5, patients received placebo, flexible doses of dronabinol 10 to 20 mg, ondansetron 8 to 16 mg, or dronabinol 10 to 20 mg and ondansetron 8 to 16 mg. The primary outcome was a total response (TR) of nausea intensity < 5 mm on visual analog scale, no vomiting/retching and no use of rescue antiemetic. The TR was similar for the active treatments: dronabinol (54%), ondansetron (58%), and combination (47%) versus placebo (20%). Nausea absence was significantly greater for the active treatment groups versus placebo (15%): dronabinol (71%), ondansetron (64%), and combination (53%; p<0.05 for all). Nausea intensity and vomiting/retching were lowest in patients treated with dronabinol. Dronabinol or ondansetron were similarly effective for the treatment of CINV. Combination therapy with dronabinol and ondansetron was not more effective than either agent alone. All active treatments were well tolerated. The population size is the greatest limitation of these data.

orally disintegrating ondansetron (Zofran ODT) versus conventional tablet formulation of ondansetron (Zofran)

Due to a lack of other available data, this study has been included. The efficacy of ondansetron ODT was compared to the conventional oral tablet of ondansetron in controlling N/V among breast cancer patients receiving high-dose epirubicin.[239] In a randomized trial, 134 patients received ondansetron ODT 8 mg twice daily or ondansetron tablet 8 mg twice daily, both for 3 days. Ondansetron tablet was significantly better at controlling emesis (72% versus 52%, respectively; p=0.02) and statistically insignificant when attempting to control nausea (66% versus 48%, respectively; p=0.054) compared to ondansetron ODT. However, when looking at major control of emesis (as having 0 to 2 emetic episodes during the 3 days) between the conventional ondansetron tablet versus ondansetron ODT, there was no real difference (76% versus 70%, respectively; p=0.28). For control of major emesis and nausea, there are no major differences between the formulations.

ondansetron (Zofran) versus transdermal scopolamine (Transderm-Scop)

A randomized, double blind, multicenter trial of 620 at-risk female patients undergoing outpatient laparoscopic or breast augmentation surgery was conducted to compare the impact of combination therapy versus monotherapy in the reduction of post-operative N/V.[240] Patients received either an active transdermal scopolamine patch or a placebo patch 2 hours before entering the operating room. Patients also received ondansetron 4 mg shortly before induction of anesthesia. Response to antiemetics, time to rescue antiemetics, number of doses of rescue antiemetics, and severity and number of nausea and vomiting episodes were recorded. The combination of transdermal scopolamine and ondansetron statistically significantly reduced nausea and vomiting compared with ondansetron alone 24 hours after surgery. However, the same observations were not applicable at 48 hours post surgery. The proportion of patients who did not experience vomiting and did not use rescue medication was 48% for the combination group and 39% for the ondansetron group (p<0.02). Total response (no nausea, no vomiting/retching, and no use of rescue medication) was also statistically higher for the combination group compared with the ondansetron-only group (35% versus 25%; p<0.01). The time to first nausea, vomiting/retching, or rescue episode was statistically significantly longer for the combination group compared with the ondansetron-only group (p<0.05).

ondansetron (Zofran) versus metoclopramide (Reglan) versus promethazine (Phenergan)

A randomized, placebo-controlled, double-blind superiority trial comparing ondansetron, metoclopramide, promethazine, and saline was conducted in 180 adult emergency room patients to assess the nausea reduction of ondansetron.[241] Nausea was evaluated on a 100-mm VAS at baseline and then 30 minutes after treatment. Patients who have a VAS score of 40-mm or more were randomized to receive intravenous ondansetron 4 mg, metoclopramide 10mg, promethazine 12.5 mg, or saline in approximately 500 mL of saline hydration. A VAS reduction of 12-mm was considered clinically significant. There were 163 patients that completed the study with a median age of 32 years old and 68% were female. The median VAS reductions for ondansetron, metoclopramide, promethazine, and saline were -22, -30, -29, and -16, respectively, using the Kruskal-Wallis test (p=0.16). The study concluded that no evidence existed proving ondansetron was superior to metoclopramide and promethazine in the reduction of nausea in adult emergency room patients however early termination may have limited the detection of ondansetron's superiority over saline.

ondansetron (Zofran) versus palonosetron (Aloxi)

A prospective randomized, double-blind trial comparing ondansetron and palonosetron was conducted in 100 adult female patients undergoing total thyroidectomy to assess nausea and vomiting, severity of nausea, use of post-operative nausea and pain rescue medication, severity of pain, and side effects at 0 to 2 hours and 2 to 24 hours post-operation.[242] With the exception of the study drugs all medications used during the surgery and in the patient-controlled analgesia (PCA) pump after surgery were the same between the 2 groups. After the surgery, patients were randomized to receive a bolus of 8 mg ondansetron (n=50) and 16 mg added to the PCA or a bolus of 0.075 mg palonosetron (n=50) and 8 mL of normal saline added to the PCA. Patients were allowed rescue metoclopramide and meperidine, as needed, for nausea and vomiting and pain, respectively. At 0 to 2 hours post-operation there were no significant differences in the incidence of nausea and vomiting between the ondansetron and palonosetron groups. However, from 2 to 24 hours post-operation the incidence of nausea and vomiting was lower in the palonosetron group compared to the ondansetron group (p=0.03). The use of rescue anti-emetics was also lower in the palonosetron group versus the ondansetron group, 10% versus 28%, respectively, during the 2 to 24 hour study period (p=0.02). Overall, during the 24 hour post-operative period the incidence of nausea and vomiting was lower in the palonosetron versus ondansetron group (42% versus 62%; p=0.045). There was not a significant difference in pain or side effects between the palonosetron and ondansetron groups. The study concluded that a bolus injection of palonosetron was more effective than combination bolus and intravenous ondansetron 2 to 24 hours post-operation for patients at high risk for post-operative nausea and vomiting.

netupitant/palonosetron (Akynzeo) versus palonosetron

A randomized, parallel-group, double-blind, multicenter trial compared a single oral dose of netupitant/palonosetron to a single oral dose of palonosetron in cancer patients receiving a chemotherapy regimen that included cisplatin.[243] The efficacy of netupitant/palonosetron was assessed in 135 patients who received netupitant/palonosetron (netupitant 300 mg and palonosetron 0.5 mg) and 136 patients who received oral palonosetron 0.5 mg. Patients in the netupitant/palonosetron group also received dexamethasone 12 mg on day 1 and dexamethasone 8 mg once daily on days 2 through 4. Patients in the palonosetron group received dexamethasone 20 mg on day 1 and dexamethasone 8 mg twice daily on days 2 through 4. The key efficacy endpoints were the percentage of patients with a complete response (CR) (defined as no emetic episode and no use of rescue medication) for the 25 to 120 hour interval (delayed phase), CR for the 0 to 24 hour interval (acute phase), and CR within 120 hours (overall phase) after the start of the chemotherapy administration. Netupitant/palonosetron had a statistically significant increase in the percentage of patients achieving CR in all 3 phases when compared to palonosetron. The netupitant/palonosetron group had a CR in the delayed phase of 90.4% versus 80.1% (p=0.032) in the palonosetron group. The netupitant/palonosetron group had a CR in the acute phase of 98.5% versus 89.7% (p=0.002) in the palonosetron group. The netupitant/palonosetron group had a CR in the overall phase of 89.6% versus 76.5% (p=0.003) in the palonosetron group.

netupitant/palonosetron (Akynzeo) versus palonosetron

A randomized, parallel-group, double-blind, multicenter trial was conducted that compared a single oral dose of netupitant/palonosetron to a single oral dose of palonosetron 0.5 mg in cancer patients scheduled to receive the first cycle of an anthracycline and cyclophosphamide (AC) regimen for the

treatment of a solid malignant tumor [244,245] All patients received a single oral dose of dexamethasone. After completion of cycle 1, patients had the option to participate in a multiple-cycle extension, receiving the same treatment as assigned in cycle 1. A total of 1,450 patients (netupitant 300 mg/palonosetron 0.5 mg, n=725; palonosetron 0.5 mg n=725) received study medication: of these, 1,438 patients (98.8%) completed cycle 1 and 1,286 patients (88.4%) continued treatment in the multiple-cycle extension. The primary efficacy endpoint was the percentage of patients achieving CR in the delayed phase, 25 to 120 hours after the start of chemotherapy administration and the major secondary efficacy endpoints included the percentage of patients achieving CR in the acute and overall phases. Netupitant/palonosetron had a statistically significant increase in the percentage of patients achieving CR in the delayed phase and both secondary endpoints of the percentage of patients achieving CR in the acute phase and overall phase. The netupitant/palonosetron group had a CR in the delayed phase of 76.9% versus 69.5% (p=0.001) in the palonosetron group. The netupitant/palonosetron group had a CR in the acute phase of 88.4% versus 85% (p=0.047) in the palonosetron group. The netupitant/palonosetron group had a CR in the overall phase of 74.3% versus 66.6% (p=0.003) in the palonosetron group.

doxylamine/pyridoxine (Diclegis) versus placebo

A randomized, double-blind, placebo-controlled study was conducted to support the safety and efficacy of doxylamine/pyridoxine in the treatment of nausea and vomiting of pregnancy.[246,247] Women (n=256) 18 years of age or older and 7 to 14 weeks gestation with nausea and vomiting of pregnancy were randomized to 14 days of doxylamine/pyridoxine or placebo. Two tablets of doxylamine/pyridoxine were administered at bedtime on day 1. If symptoms of nausea and vomiting persisted into the afternoon hours of day 2, the patient could begin taking 1 tablet in the morning on day 3 in addition to 2 tablets at bedtime. If symptoms persisted on day 4, the patient could take an additional tablet in the afternoon. A maximum of 4 tablets (1 in the morning, 1 in the afternoon and 2 at bedtime) were taken daily. Over the treatment period, 19% of doxylamine/pyridoxine treated patients remained on 2 tablets daily, 21% received 3 tablets daily, and 60% received 4 tablets daily. The primary efficacy endpoint was the change from baseline at day 15 in the Pregnancy Unique-Quantification of Emesis (PUQE) score. The PUQE score incorporates the number of daily vomiting episodes, number of daily heaves, and length of daily nausea in hours, for an overall score of symptoms rated from 3 (no symptoms) to 15 (most severe). At baseline, the mean PUQE score was 9 in the doxylamine/pyridoxine arm and 8.8 in the placebo arm. There was a 0.7 (95% CI, 0.2 to 1.2;p=0.006) mean decrease from baseline in PUQE score at day 15 with doxylamine/pyridoxine compared to placebo. The only adverse effect that occurred in more than 5% of patients and exceeded the placebo rate was somnolence which occurred in 14.9% of patients in the doxylamine/pyridoxine group compared to 11.7% in the placebo group.

META-ANALYSES

A meta-analysis compared the efficacy and safety of palonosetron with other 5-HT_3 receptor antagonists (dolasetron, ondansetron, granisetron) for prevention of chemotherapy induced nausea and vomiting (CINV).[248] The cumulative incidences of emesis were significantly lower in the patients treated with palonosetron on the first day (relative risk [RR], 1.11; 95% CI, 1.05 to 1.17), from 2 to 5 days (RR, 1.26; 95% CI, 1.16 to 1.36) and the overall 5 days (RR, 1.23; 95% CI, 1.13 to 1.34). No differences were found in safety. Another meta-analysis found similar results (5 studies; n=2,057) comparing palonosetron to ondansetron, granisetron, and dolasetron.[249] They found that palonosetron

resulted in less nausea, both acute (RR, 0.86; 95% CI, 0.76 to 0.96; p=0.007) and delayed (RR, 0.82; 95% CI, 0.75 to 0.89; p<0.00001). Patients using palonosetron also had less acute vomiting (RR, 0.76; 95% CI, 0.66 to 0.88; p=0.0002) and delayed vomiting (RR, 0.76; 95% CI, 0.68 to 0.85; p<0.00001) compared to the other 5-HT_3 receptor antagonists. An earlier meta-analysis did not find a difference between granisetron, ondansetron, and dolasetron.[250]

Multiple meta-analyses have compared the efficacy of 5-HT_3 receptor antagonists in post-operative nausea and vomiting (PONV). One meta-analysis compared the efficacy of ondansetron and granisetron in early and total PONV. The risk ratio (RR) of ondansetron compared to granisetron in early PONV was 1.25, but it was not statistically significant (95% CI, 0.82 to 0.92; p=0.31). Likewise, the RR of ondansetron compared to granisetron in overall PONV was 1.13, but it was also not significant (95% CI, 0.82 to 1.56; p=0.46). Thus, the authors concluded that both agents were equally effective.[251] A network meta-analysis compared the efficacy of three 5-HT_3 receptor antagonists (ondansetron, granisetron, and dolasetron) during the first 24 hours for PONV prophylaxis (85 studies; n=15,269).[252] The authors found that granisetron was superior to ondansetron (odds ratio [OR], 1.53; 95% CI, 1.15 to 2) and dolasetron (OR, 1.67; 95% CI, 1.12 to 2.38). Efficacy was similar among agents for vomiting and all agents were found to be superior to placebo.

A pairwise and network meta-analysis of 450 studies (n=80,410) assessed the efficacy of 5-HT_3 receptor antagonists for post-operative nausea and vomiting.[253] Overall, the following treatments were all considered effective compared to placebo for reduction of vomiting, with the exception of palonosetron and dexamethasone (OR, 1.43 [95% CI, 0.2 to 10.14]): ondansetron plus droperidol IV, granisetron plus dexamethasone, ondansetron plus metoclopramide IV, ondansetron plus dexamethasone, dolasetron plus dexamethasone, dolasetron plus droperidol IV, granisetron, granisetron plus droperidol IV, ondansetron, palonosetron, and dolasetron (238 trials; n=12,781; all OR < 1 and 95% CI < 1). Overall, the following treatments were all considered effective compared to placebo for the reduction of nausea, with the exceptions of palonosetron and dexamethasone (OR, 0.37 [95% CI, 0.12 to 1.1]) and metoclopramide IV plus ondansetron (OR, 0.3 [95% CI, 0.07 to 1.37]): dolasetron plus droperidol IV, granisetron plus dexamethasone, granisetron plus droperidol IV, dolasetron plus dexamethasone, ondansetron plus droperidol IV, ondansetron plus dexamethasone, palonosetron, granisetron, ondansetron, and dolasetron (195 trials; n=24,230; all OR < 1 and 95% CI < 1). All agents were more effective than placebo for post-operative nausea and vomiting (125 trials; n=16,667; all OR < 1 and 95% CI < 1). The same pairwise and network meta-analysis of 31 studies (n=6,623) metaanalysis found that significantly more patients receiving granisetron plus dexamethasone experienced an arrhythmia compared to placebo (OR, 2.96; 95% CI, 1.11 to 7.94) than other 5-HT_3 receptor antagonists (dolasetron: OR, 0.68 [95% CI, 0.44 to 1.04] and ondansetron plus dexamethasone: OR, 0.52 [95% CI, 0.16 to 1.68]).[254]

Ondansetron has demonstrated superiority over metoclopramide in another meta-analysis comparing the efficacy in PONV within 24 hours following laparoscopic cholecystectomy (OR, 0.33; 95% CI, 0.22 to 0.49; p<0.00001.[255] A Cochrane review found that droperidol, metoclopramide, dolasetron, dexamethasone, and granisetron were all superior to placebo (RR varied from 0.6 to 0.8), but also noted that the results may have been affected by publication bias (737 studies; n=103,237).[256]

SUMMARY

The 5-HT_3 antagonists offer significant advantages in the prevention of nausea and vomiting (N/V) due to chemotherapy and radiotherapy. Based on available data, there appears to be little significant

difference among the drugs in this class The National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) do not recommend one over another, except in the case of moderately emetogenic chemotherapy, in which ASCO recommends palonosetron (Aloxi) as the preferred 5-HT_3 antagonist. Granisetron transdermal (Sancuso) may offer benefit to select patients undergoing moderate to highly emetogenic chemotherapy regimens who cannot tolerate other formulations. The transdermal formulation did demonstrate non-inferiority in efficacy to the oral formulation of granisetron. The ondansetron oral soluble film (Zuplenz) has demonstrated bioavailability similar to that of the orally disintegrating dosage form of ondansetron (Zofran ODT).

Aprepitant (Emend), which must be taken for 3 days, can be used in combination with either dexamethasone or a 5-HT_3 receptor antagonist when treating chemotherapy-induced N/V or for use as monotherapy in prevention of post-operative N/V, but its effectiveness has not been compared to other agents for these uses. The intravenous formulation of Emend, fosaprepitant, is dosed on day 1 only. The newest NK_1 receptor antagonist, rolapitant (Varubi), also is dosed once on day 1 of chemotherapy for either highly or moderately emetogenic chemotherapy regimens. Netupitant/palonosetron (Akynzeo) offers a single capsule dosage combination of a substance P/NK_1 receptor antagonist and a 5-HT_3 receptor antagonist taken on the day of chemotherapy. The synthetic cannabinoids are recommended as second-line therapy for chemotherapy induced N/V when patients fail to respond adequately to conventional antiemetics. The significant risk for abuse and misuse, increased potential for drug interactions, and increased risk for psychotomimetic reactions that has not been observed with other oral antiemetics suggest the cannabinoids should be monitored closely and reserved for specific use only.

There are both non-pharmacologic and pharmacologic interventions for the prevention or management of motion sickness. None are ideal, and the medications used including antihistamines, phenothiazines and anticholinergics typically cause drowsiness or similar adverse effects.

Doxylamine/pyridoxine (Diclegis) is the only medication approved for the treatment of N/V of pregnancy in women who do not respond to conservative management. It is pregnancy category A. Doxylamine/pyridoxine is associated with significant sedation.

REFERENCES

1 Emend [package insert]. Whitehouse Station, NJ; Merck & Co.; December 2015.
2 Emend for injection [package insert]. Whitehouse Station, NJ; Merck & Co.; October 2014.
3 Varubi [package insert]. Waltham, MA; Tesaro; September 2015.
4 Anzemet tablets [package insert]. Bridgewater, NJ; Sanofi-Aventis; September 2014.
5 Anzemet injection [package insert]. Bridgewater, NJ; Sanofi-Aventis; October 2014.
6 Granisol [package insert]. Madison, MS; PediatRx; November 2010.
7 Kytril [package insert]. South San Francisco, CA; Genentech; April 2011.
8 Sancuso [package insert]. Bridgewater, NJ; ProStrakan; September 2015.
9 Zofran [package insert]. Research Triangle Park, NC; GlaxoSmithKline; September 2014.
10 Zuplenz [package insert]. Portland, OR; Galena; September 2014.
11 Zofran injection [package insert]. Research Triangle Park, NC; GlaxoSmithKline; September 2014.
12 Aloxi IV [package insert]. Woodcliff Lake, NJ; Helsinn/Eisai; September 2014.
13 Akynzeo [package insert]. Woodcliff Lake, NJ; Eisai; April 2015.
14 Marinol [package insert]. Marietta, GA; AbbVie; August 2015.
15 Cesamet [package insert]. Costa Mesa, CA; Valeant; September 2013.
16 Metozolv ODT [package insert]. Morrisville, NC; Salix; December 2011.
17 Available at: www.drugs.com. Accessed January 22, 2016.
18 Available at: www.clinicalpharmacology.com. Accessed January 22, 2016.
19 Reglan [package insert]. Baudette, MN; Ani; September 2013.
20 Diclegis [package insert]. Bryn Mawr, PA; Duchesnay; April 2013.
21 Available at: www.drugs.com. Accessed January 22, 2016.

22 Available at: www.clinicalpharmacology.com. Accessed January 22, 2016.
23 Tigan injectable [package insert]. Spring Valley, NY; Par; February 2015.
24 Tigan [package insert]. New York, NY; Pfizer; April 2008.
25 Available at: www.drugs.com. Accessed January 22, 2016.
26 Available at: www.clinicalpharmacology.com. Accessed January 22, 2016.
27 Available at: www.drugs.com. Accessed January 22, 2016.
28 Available at: www.clinicalpharmacology.com. Accessed January 22, 2016.
29 Transderm Scop [package insert]. Parsippany, NJ; Novartis; April 2013.
30 Ettinger DS, Berger MJ. Aston J, et al. NCCN Clinical Practice guidelines in oncology: antiemesis, version 2.2105. Available at: http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf. Accessed January 22, 2016.
31 Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2011; 29(31): 4189-4198. DOI: 10.1200/JCO.2010.34.4614. Available at: http://jco.ascopubs.org/content/29/31/4189.full.pdf+html. Accessed January 22, 2016.
32 Ettinger DS, Berger MJ. Aston J, et al. NCCN Clinical Practice guidelines in oncology: antiemesis, version 2.2105. Available at: http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf. Accessed January 22, 2016.
33 Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2011; 29(31): 4189-4198. DOI: 10.1200/JCO.2010.34.4614. Available at: http://jco.ascopubs.org/content/29/31/4189.full.pdf+html. Accessed January 22, 2016.
34 Ettinger DS, Berger MJ. Aston J, et al. NCCN Clinical Practice guidelines in oncology: antiemesis, version 2.2105. Available at: http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf. Accessed January 22, 2016.
35 Fetting JH, Grochow LB, Folstein MF, et al. The course of nausea and vomiting after high-dose cyclophosphamide. Cancer Treat Rep. 1982; 66:1487–1493.
36 Morrow GR. A patient report measure for the quantification of chemotherapy induced nausea and emesis: Psychometric properties of the Morrow Assessment of Nausea and Emesis (MANE). Br J Cancer. 1992; 19:S72–S74 (suppl).
37 Willan A, Warr D, Pater J, et al. Methodological issues and antiemetic studies. In Osoba D, ed. Effect of Cancer on Quality of Life. Boca Raton, FL: CRC Press; 1991; 229–249.
38 Clark R, Tyson L, Frisone M. A correlation of objective (OBJ) and subjective (SUBJ) parameters in assessing antiemetic regimens (AER). Oncol Nurs Forum. 1985; 12:96(suppl).
39 Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2011; 29(31): 4189-4198. DOI: 10.1200/JCO.2010.34.4614. Available at: http://jco.ascopubs.org/content/29/31/4189.full.pdf+html. Accessed January 22, 2016.
40 Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2011; 29(31): 4189-4198. DOI: 10.1200/JCO.2010.34.4614. Available at: http://jco.ascopubs.org/content/29/31/4189.full.pdf+html. Accessed January 22, 2016.
41 Ettinger DS, Berger MJ. Aston J, et al. NCCN Clinical Practice guidelines in oncology: antiemesis, version 2.2105. Available at: http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf. Accessed January 22, 2016.
42 Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2011; 29(31): 4189-4198. DOI: 10.1200/JCO.2010.34.4614. Available at: http://jco.ascopubs.org/content/29/31/4189.full.pdf+html. Accessed January 22, 2016.
43 Hesketh PJ, Bohlke K, Lyman GH, et al. Antiemetics: American Society of Clinical Oncology focused guideline update. J Clin Oncol. 2015. DOI: JCO.2015.64.3635. [Epub ahead of print]. Available at: http://www.instituteforquality.org/antiemetics-asco-clinical-practice-guideline-update. Accessed Janaury 22, 2016.
44 Ettinger DS, Berger MJ. Aston J, et al. NCCN Clinical Practice guidelines in oncology: antiemesis, version 2.2105. Available at: http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf. Accessed January 22, 2016.
45 Available at: http://wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/motion-sickness.aspx. Accessed January 22, 2016.
46 Diclegis for nausea and vomiting of pregnancy. The Med Ltr Drugs Ther. Aug. 5, 2013; 1422: 61.
47 American College of Obstetricians and Gynecologists. Nausea and vomiting of pregnancy. ACOG Practice Bulletin No. 52. Obstet Gynecol. 2015; 126 (3):e12-24.
48 Association of Professors of Gynecology and Obstetrics. Nausea and vomiting of pregnancy. APGO continuing series on women's health education. April 2015. Available at: https://www.apgo.org/education/women/nausea-and-vomiting-of-pregnancy.html Accessed January 22, 2016.
49 Diclegis for nausea and vomiting in pregnancy. Med Lett Drugs Ther. 2013; 55(1422): 61-62. Available at: http://secure.medicalletter.org/TML-article-1422a. Accessed January 22, 2016..
50 Emend [package insert]. Whitehouse Station, NJ; Merck & Co.; December 2015.
51 Emend for injection [package insert]. Whitehouse Station, NJ; Merck & Co.; October 2014.
52 Varubi [package insert]. Waltham, MA; Tesaro; September 2015.
53 Anzemet tablets [package insert]. Bridgewater, NJ; Sanofi-Aventis; September 2014.
54 Anzemet injection [package insert]. Bridgewater, NJ; Sanofi-Aventis; October 2014.
55 Granisol [package insert]. Madison, MS; PediatRx; November 2010.
56 Kytril [package insert]. South San Francisco, CA; Genentech; April 2011.
57 Sancuso [package insert]. Bridgewater, NJ; ProStrakan; September 2015.
58 Zofran [package insert]. Research Triangle Park, NC; GlaxoSmithKline; September 2014.
59 Zuplenz [package insert]. Portland, OR; Galena; September 2014.
60 Zofran injection [package insert]. Research Triangle Park, NC; GlaxoSmithKline; September 2014.
61 Aloxi IV [package insert]. Woodcliff Lake, NJ; Helsinn/Eisai; September 2014.
62 Akynzeo [package insert]. Woodcliff Lake, NJ; Eisai; April 2015.
63 Marinol [package insert]. Marietta, GA; AbbVie; August 2015.
64 Cesamet [package insert]. Costa Mesa, CA; Valeant; September 2013.
65 Metozolv ODT [package insert]. Morrisville, NC; Salix; December 2011.
66 Reglan [package insert]. Baudette, MN; Ani; September 2013.
67 Diclegis [package insert]. Bryn Mawr, PA; Duchesnay; April 2013.
68 Tigan injectable [package insert]. Spring Valley, NY; Par; February 2015.

69 Tigan [package insert]. New York, NY; Pfizer; April 2008.
70 Transderm Scop [package insert]. Parsippany, NJ; Novartis; April 2013.
71 Available at: www.drugs.com. Accessed January 22, 2016.
72 Available at: www.clinicalpharmacology.com. Accessed January 22, 2016.
73 Armstrong DM, Pickel VM, Joh TH, et al. Immunocytochemical localization of catecholamine synthesizing enzymes and neuropeptides in area postrema and medial nucleus tractus solitarius of rat brain. J Comp Neurol. 1982; 196:505–517.
74 Meller D, Vincent M. The emerging role of cannabinoid neuromodulators in symptom management. Support Care Cancer. 2007; 15: 63–71.
75 Emend [package insert]. Whitehouse Station, NJ; Merck & Co.; December 2015.
76 Emend for injection [package insert]. Whitehouse Station, NJ; Merck & Co.; October 2014.
77 Varubi [package insert]. Waltham, MA; Tesaro; September 2015.
78 Anzemet tablets [package insert]. Bridgewater, NJ; Sanofi-Aventis; September 2014.
79 Anzemet injection [package insert]. Bridgewater, NJ; Sanofi-Aventis; October 2014.
80 Granisol [package insert]. Madison, MS; PediatRx; November 2010.
81 Kytril [package insert]. South San Francisco, CA; Genentech; April 2011.
82 Sancuso [package insert]. Bridgewater, NJ; ProStrakan; September 2015.
83 Zofran [package insert]. Research Triangle Park, NC; GlaxoSmithKline; September 2014.
84 Zuplenz [package insert]. Portland, OR; Galena; September 2014.
85 Zofran injection [package insert]. Research Triangle Park, NC; GlaxoSmithKline; September 2014.
86 Aloxi IV [package insert]. Woodcliff Lake, NJ; Helsinn/Eisai; September 2014.
87 Akynzeo [package insert]. Woodcliff Lake, NJ; Eisai; April 2015.
88 Marinol [package insert]. Marietta, GA; AbbVie; August 2015.
89 Cesamet [package insert]. Costa Mesa, CA; Valeant; September 2013.
90 Metozolv ODT [package insert]. Morrisville, NC; Salix; December 2011.
91 Reglan [package insert]. Baudette, MN; Ani; September 2013.
92 Diclegis [package insert]. Bryn Mawr, PA; Duchesnay; April 2013.
93 Tigan injectable [package insert]. Spring Valley, NY; Par; February 2015.
94 Tigan [package insert]. New York, NY; Pfizer; April 2008.
95 Transderm Scop [package insert]. Parsippany, NJ; Novartis; April 2013.
96 Available at: www.drugs.com. Accessed January 22, 2016.
97 Available at: www.clinicalpharmacology.com. Accessed January 22, 2016.
98 Emend [package insert]. Whitehouse Station, NJ; Merck & Co.; December 2015.
99 Emend for injection [package insert]. Whitehouse Station, NJ; Merck & Co.; October 2014.
100 Varubi [package insert]. Waltham, MA; Tesaro; September 2015.
101 Anzemet tablets [package insert]. Bridgewater, NJ; Sanofi-Aventis; September 2014.
102 Anzemet injection [package insert]. Bridgewater, NJ; Sanofi-Aventis; October 2014.
103 Granisol [package insert]. Madison, MS; PediatRx; November 2010.
104 Kytril [package insert]. South San Francisco, CA; Genentech; April 2011.
105 Sancuso [package insert]. Bridgewater, NJ; ProStrakan; September 2015.
106 Zofran [package insert]. Research Triangle Park, NC; GlaxoSmithKline; September 2014.
107 Zuplenz [package insert]. Portland, OR; Galena; September 2014.
108 Zofran injection [package insert]. Research Triangle Park, NC; GlaxoSmithKline; September 2014.
109 Aloxi IV [package insert]. Woodcliff Lake, NJ; Helsinn/Eisai; September 2014.
110 Akynzeo [package insert]. Woodcliff Lake, NJ; Eisai; April 2015.
111 Marinol [package insert]. Marietta, GA; AbbVie; August 2015.
112 Cesamet [package insert]. Costa Mesa, CA; Valeant; September 2013.
113 Metozolv ODT [package insert]. Morrisville, NC; Salix; December 2011.
114 Reglan [package insert]. Baudette, MN; Ani; September 2013.
115 Diclegis [package insert]. Bryn Mawr, PA; Duchesnay; April 2013.
116 Tigan injectable [package insert]. Spring Valley, NY; Par; February 2015.
117 Tigan [package insert]. New York, NY; Pfizer; April 2008.
118 Transderm Scop [package insert]. Parsippany, NJ; Novartis; April 2013.
119 Available at: www.drugs.com. Accessed January 22, 2016.
120 Available at: www.clinicalpharmacology.com. Accessed January 22, 2016.
121 Emend [package insert]. Whitehouse Station, NJ; Merck & Co.; December 2015.
122 Emend for injection [package insert]. Whitehouse Station, NJ; Merck & Co.; October 2014.
123 Varubi [package insert]. Waltham, MA; Tesaro; September 2015.
124 Anzemet tablets [package insert]. Bridgewater, NJ; Sanofi-Aventis; September 2014.
125 Anzemet injection [package insert]. Bridgewater, NJ; Sanofi-Aventis; October 2014.
126 Granisol [package insert]. Madison, MS; PediatRx; November 2010.
127 Kytril [package insert]. South San Francisco, CA; Genentech; April 2011.
128 Sancuso [package insert]. Bridgewater, NJ; ProStrakan; September 2015.
129 Zofran [package insert]. Research Triangle Park, NC; GlaxoSmithKline; September 2014.
130 Zuplenz [package insert]. Portland, OR; Galena; September 2014.
131 Zofran injection [package insert]. Research Triangle Park, NC; GlaxoSmithKline; September 2014.
132 Aloxi IV [package insert]. Woodcliff Lake, NJ; Helsinn/Eisai; September 2014.
133 Akynzeo [package insert]. Woodcliff Lake, NJ; Eisai; April 2015.
134 Marinol [package insert]. Marietta, GA; AbbVie; August 2015.

135 Cesamet [package insert]. Costa Mesa, CA; Valeant; September 2013.
136 Metozolv ODT [package insert]. Morrisville, NC; Salix; December 2011.
137 Reglan [package insert]. Baudette, MN; Ani; September 2013.
138 Diclegis [package insert]. Bryn Mawr, PA; Duchesnay; April 2013.
139 Tigan injectable [package insert]. Spring Valley, NY; Par; February 2015.
140 Tigan [package insert]. New York, NY; Pfizer; April 2008.
141 Transderm Scop [package insert]. Parsippany, NJ; Novartis; April 2013.
142 Available at: www.drugs.com. Accessed January 22, 2016.
143 Available at: www.clinicalpharmacology.com. Accessed January 22, 2016.
144 McCrea JB, Majumdar AK, Goldberg MR, et al. Effects of the neurokinin1 receptor antagonist aprepitant on the pharmacokinetics of dexamethasone and methylprednisolone. Clin Pharmacol Ther. 2003; 74:17-24.
145 Emend [package insert]. Whitehouse Station, NJ; Merck & Co.; December 2015.
146 Emend for injection [package insert]. Whitehouse Station, NJ; Merck & Co.; October 2014.
147 Varubi [package insert]. Waltham, MA; Tesaro; September 2015.
148 Anzemet tablets [package insert]. Bridgewater, NJ; Sanofi-Aventis; September 2014.
149 Anzemet injection [package insert]. Bridgewater, NJ; Sanofi-Aventis; October 2014.
150 Granisol [package insert]. Madison, MS; PediatRx; November 2010.
151 Kytril [package insert]. South San Francisco, CA; Genentech; April 2011.
152 Sancuso [package insert]. Bridgewater, NJ; ProStrakan; September 2015.
153 Zofran [package insert]. Research Triangle Park, NC; GlaxoSmithKline; September 2014.
154 Zuplenz [package insert]. Portland, OR; Galena; September 2014.
155 Zofran injection [package insert]. Research Triangle Park, NC; GlaxoSmithKline; September 2014.
156 Aloxi IV [package insert]. Woodcliff Lake, NJ; Helsinn/Eisai; September 2014.
157 Akynzeo [package insert]. Woodcliff Lake, NJ; Eisai; April 2015.
158 Marinol [package insert]. Marietta, GA; AbbVie; August 2015.
159 Cesamet [package insert]. Costa Mesa, CA; Valeant; September 2013.
160 Metozolv ODT [package insert]. Morrisville, NC; Salix; December 2011.
161 Reglan [package insert]. Baudette, MN; Ani; September 2013.
162 Diclegis [package insert]. Bryn Mawr, PA; Duchesnay; April 2013.
163 Tigan injectable [package insert]. Spring Valley, NY; Par; February 2015.
164 Tigan [package insert]. New York, NY; Pfizer; April 2008.
165 Transderm Scop [package insert]. Parsippany, NJ; Novartis; April 2013.
166 Available at: www.drugs.com. Accessed January 22, 2016.
167 Available at: www.clinicalpharmacology.com. Accessed January 22, 2016.
168 Emend [package insert]. Whitehouse Station, NJ; Merck & Co.; December 2015.
169 Emend for injection [package insert]. Whitehouse Station, NJ; Merck & Co.; October 2014.
170 Varubi [package insert]. Waltham, MA; Tesaro; September 2015.
171 Anzemet tablets [package insert]. Bridgewater, NJ; Sanofi-Aventis; September 2014.
172 Anzemet injection [package insert]. Bridgewater, NJ; Sanofi-Aventis; October 2014.
173 Granisol [package insert]. Madison, MS; PediatRx; November 2010.
174 Kytril [package insert]. South San Francisco, CA; Genentech; April 2011.
175 Sancuso [package insert]. Bridgewater, NJ; ProStrakan; September 2015.
176 Zofran [package insert]. Research Triangle Park, NC; GlaxoSmithKline; September 2014.
177 Zuplenz [package insert]. Portland, OR; Galena; September 2014.
178 Zofran injection [package insert]. Research Triangle Park, NC; GlaxoSmithKline; September 2014.
179 Aloxi IV [package insert]. Woodcliff Lake, NJ; Helsinn/Eisai; September 2014.
180 Akynzeo [package insert]. Woodcliff Lake, NJ; Eisai; April 2015.
181 Marinol [package insert]. Marietta, GA; AbbVie; August 2015.
182 Cesamet [package insert]. Costa Mesa, CA; Valeant; September 2013.
183 Metozolv ODT [package insert]. Morrisville, NC; Salix; December 2011.
184 Reglan [package insert]. Baudette, MN; Ani; September 2013.
185 Diclegis [package insert]. Bryn Mawr, PA; Duchesnay; April 2013.
186 Tigan injectable [package insert]. Spring Valley, NY; Par; February 2015.
187 Tigan [package insert]. New York, NY; Pfizer; April 2008.
188 Transderm Scop [package insert]. Parsippany, NJ; Novartis; April 2013.
189 Available at: www.drugs.com. Accessed January 22, 2016.
190 Available at: www.clinicalpharmacology.com. Accessed January 22, 2016.
191 Karamanlioglu B, Turan A, Memis D, et al. Comparison of oral dolasetron and ondansetron in the prophylaxis of postoperative nausea and vomiting in children. Eur J Anaesthesiol. 2003; 20(10):831-835.
192 Fujii Y, Tanaka H, Ito M. Preoperative oral granisetron for the prevention of vomiting after strabismus surgery in children. Ophthalmology. 1999; 106(9):1713–1715.
193 Fujii Y, Saitoh Y, Tanaka H, et al. Preoperative oral antiemetics for reducing postoperative vomiting after tonsillectomy in children: granisetron versus perphenazine. Anesth Analg. 1999; 88(6):1298-1301.
194 Fujii Y, Toyooka H, Tanaka H. Oral granisetron prevents postoperative vomiting in children. Br J Anaesth. 1998; 81(3):390–392.
195 Phillips RS, Gopaul S, Gibson F, et al. Antiemetic medication for prevention and treatment of chemotherapy induced nausea and vomiting in childhood. Cochrane Database Syst Rev. 2010; 9: CD007786. DOI: 10.1002/14651858.CD007786.pub2.

196 Kang HJ, Loftus S, Taylor A, et al. Aprepitant for the prevention of chemotherapy-induced nausea and vomiting in children: a randomised, double-blind, phase 3 trial. Lancet Oncol. 2015; 16(4): 385-394. DOI: 10.1016/S1470-2045(15)70061-6.
197 Drugs@FDA. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed January 22, 2016.
198 Basch E, Prestrud AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol. 2011; 29(31): 4189-4198. DOI: 10.1200/JCO.2010.34.4614. Available at: http://jco.ascopubs.org/content/29/31/4189.full.pdf+html. Accessed January 22, 2016.
199 Hesketh PJ, Bohlke K, Lyman GH, et al. Antiemetics: American Society of Clinical Oncology focused guideline update. J Clin Oncol. 2015. DOI: JCO.2015.64.3635. [Epub ahead of print]. Available at: http://www.instituteforquality.org/antiemetics-asco-clinical-practice-guideline-update. Accessed January 22, 2016.
200 Emend [package insert]. Whitehouse Station, NJ; Merck & Co.; December 2015.
201 Emend for injection [package insert]. Whitehouse Station, NJ; Merck & Co.; October 2014.
202 Varubi [package insert]. Waltham, MA; Tesaro; September 2015.
203 Anzemet tablets [package insert]. Bridgewater, NJ; Sanofi-Aventis; September 2014.
204 Anzemet injection [package insert]. Bridgewater, NJ; Sanofi-Aventis; October 2014.
205 Granisol [package insert]. Madison, MS; PediatRx; November 2010.
206 Kytril [package insert]. South San Francisco, CA; Genentech; April 2011.
207 Sancuso [package insert]. Bridgewater, NJ; ProStrakan; September 2015.
208 Zofran [package insert]. Research Triangle Park, NC; GlaxoSmithKline; September 2014.
209 Zuplenz [package insert]. Portland, OR; Galena; September 2014.
210 Zofran injection [package insert]. Research Triangle Park, NC; GlaxoSmithKline; September 2014.
211 Aloxi IV [package insert]. Woodcliff Lake, NJ; Helsinn/Eisai; September 2014.
212 Akynzeo [package insert]. Woodcliff Lake, NJ; Eisai; April 2015.
213 Marinol [package insert]. Marietta, GA; AbbVie; August 2015.
214 Cesamet [package insert]. Costa Mesa, CA; Valeant; September 2013.
215 Metozolv ODT [package insert]. Morrisville, NC; Salix; December 2011.
216 Reglan [package insert]. Baudette, MN; Ani; September 2013.
217 Diclegis [package insert]. Bryn Mawr, PA; Duchesnay; April 2013.
218 Tigan injectable [package insert]. Spring Valley, NY; Par; February 2015.
219 Tigan [package insert]. New York, NY; Pfizer; April 2008.
220 Transderm Scop [package insert]. Parsippany, NJ; Novartis; April 2013.
221 Available at: www.drugs.com. Accessed January 22, 2016.
222 Available at: www.clinicalpharmacology.com. Accessed January 22, 2016.
223 de Wit R, Herrstedt J, Rapoport B, et al. Addition of the oral NK1 antagonist aprepitant to standard antiemetics provides protection against nausea and vomiting during multiple cycles of cisplatin-based chemotherapy. J Clin Oncol. 2003; 21(22):4105–4111.
224 Albany C, Brames M, Fausel C, et al. Randomized, double-blind, placebo-controlled, phase III cross-over study evaluating the oral neurokinin-1 antagonist aprepitant in combination with a 5HT3 receptor antagonist and dexamethasone in patients with germ cell tumors receiving 5-day cisplatin combination chemotherapy regimens: A Hoosier Oncology Group Study. J Clin Oncol. 2012; 30:3998–4003.
225 Habib AS, Keifer JC, Borel CO, et al. A comparison of the combination of aprepitant and dexamethasone versus the combination of ondansetron and dexamethasone for the prevention of postoperative nausea and vomiting in patients undergoing craniotomy. Anesth Analg. 2011; 112(4):813–8.
226 Vallejo M, Phelps A, Ibinson, J, et al. Aprepitant plus ondansetron compared with ondansetron alone in reducing postoperative nausea and vomiting in ambulatory patients undergoing plastic surgery. Plastic and Reconstructive Surgery. 2012; 129(2): 519–526.
227 Roila F, Ruggeri B, Ballatori E, et al. Aprepitant versus dexamethasone for preventing chemotherapy-induced delayed emesis in patients with breast cancer: a randomized double blind study. J Clin Oncol. 2014 Jan 10;32(2):101–6.
228 Rapoport BL, Chasen MR, Gridelli C. et a. Safety and efficacy of rolapitant for prevention of chemotherapy-induced nausea and vomiting after administration of cisplatin-based highly emetogenic chemotherapy in patients with cancer: two randomised, active-controlled, double-blind, phase 3 trials. Lancet Oncol. 2015 Sep;16(9):1079-89. DOI: 10.1016/S1470-2045(15)00035-2.
229 Schwartzberg LS, Modiano MR, Rapoport BL et al. Safety and efficacy of rolapitant for prevention of chemotherapy-induced nausea and vomiting after administration of moderately emetogenic chemotherapy or anthracycline and cyclophosphamide regimens in patients with cancer: a randomised, active-controlled, double-blind, phase 3 trial. Lancet Oncol. 2015 Sep; 16(9): 1071-8. DOI: 10.1016/S1470-2045(15)00034-0.
230 Fauser AA, Duclos B, Chemaissani A, et al. Therapeutic equivalence of single oral doses of dolasetron mesylate and multiple doses of ondansetron for the prevention of emesis after moderately emetogenic chemotherapy. European Dolasetron Comparative Study Group. Eur J Cancer. 1996; 32A:1523–1529.
231 Fox-Geiman MP, Fisher SG, Kiley K, et al. Double-blind comparative trial of oral ondansetron versus oral granisetron versus IV ondansetron in the prevention of nausea and vomiting associated with highly emetogenic preparative regimens prior to stem cell transplantation. Biol Blood Marrow Transplant. 2001; 7:596–603.
232 Noble A, Bremer K, Goedhals L, et al. A double-blind, randomized, crossover comparison of granisetron and ondansetron in 5-day fractionated chemotherapy: assessment of efficacy, safety and patient preference. The Granisetron Study Group. Eur J Cancer. 1994; 30A(8):1083–1088.
233 Candiotti KA, Nhuch F, Kamat A, et al. Granisetron versus ondansetron treatment for breakthrough postoperative nausea and vomiting after prophylactic ondansetron failure: a pilot study. Anesth Analg. 2007; 104(6):1370–1373.
234 Bhatnagar S, Gupta D, Mishra S, et al. Preemptive antiemesis in patients undergoing modified radical mastectomy: oral granisetron versus oral ondansetron in a double-blind, randomized, controlled study. J Clin Anesth. 2007; 19(7):512–516.
235 Sancuso [package insert]. Bedminster, NJ; ProStrakan Inc; September 2011.
236 Roscoe J, Heckler C, Morrow G, et al. Prevention of delayed nausea: A University of Rochester cancer center community clinical oncology program study of patients receiving chemotherapy. J Clin Oncol. 2012; 30:3389–3395.
237 Schwartzberg L, Barbour SY, Morrow GR ,et al. Pooled analysis of phase III clinical studies of palonosetron versus ondansetron, dolasetron, and granisetron in the prevention of chemotherapy-induced nausea and vomiting (CINV). Support Care Cancer. 2014 Feb;22(2):469-77. DOI: 10.1007/s00520-013-1999-9. Epub; October 19, 2013.

238 Meiri E, Jhangiani H, Vredenburgh J, et al. Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting. Curr Med Res Opin. 2007; 23(3): 533–543.
239 Pectasides D, Dafni U, Aravantions G, et al. A randomized trial to compare the efficacy and safety of antiemetic treatment with ondansetron and ondansetron zydis in patients with breast cancer treated with high-dose epirubicin. Anticancer Res. 2007; 27(6C):4411–4117.
240 Gan T, et al. A Randomized, Double-Blind, Multicenter Trial Comparing Transdermal Scopolamine Plus Ondansetron to Ondansetron Alone for the Prevention of Postoperative Nausea and Vomiting in the Outpatient Setting. Anesth Analg. 2009; 108:1498–504.
241 Barrett T, DiPersio D, Jenkins C, et al. A randomized, placebo-controlled trial of ondansetron, metoclopramide, and promethazine in adults. Am J Emerg Med. 2011; 29(3):247–255.
242 Moon Y, Joo J, Lee Y. Anti-emetic effect of ondansetron and palonosetron in thyroidectomy: a prospective, randomized, double-blind study. British Journal of Anaesthesia. 2012; 108(3): 417–422.
243 Akynzeo [package insert]. Woodcliff Lake, NJ; Eisai; April 2015.
244 Akynzeo [package insert]. Woodcliff Lake, NJ; Eisai; April 2015.
245 Aapro-Piacentini M, Rugo H, Rossi G, et al. A randomized Phase 3 study evaluating the efficacy and safety of NEPA, a fixed-dose combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy. Ann Oncol. 2014;25(7):1328–33. DOI: 10.1093/annonc/mdu101.
246 Diclegis [package insert]. Bryn Mawr, PA; Duchesnay USA; April 2013
247 Koren G, Clark S, Hankins GDV, et al. Effectiveness of delayed-release doxylamine and pyridoxine for nausea and vomiting of pregnancy: a randomized placebo controlled trial. Am J Obstet Gynecol. 2010; 203(6):571.e1-7.
248 Jin Y, Sun W, Gu D, et al. Comparative efficacy and safety of palonosetron with the first 5-HT3 receptor antagonists for the chemotherapy induced nausea and vomiting: a meta-analysis. Eur J Cancer Care. 2013; 22(1): 41-50. DOI: 10.1111/j.1365-2354.2012.01353.x.
249 Botrel TE, Clark OA, Clark L, et al. Efficacy of palonosetron (PAL) compared to other serotonin inhibitors (5-HT3R) in preventing chemotherapy-induced nausea and vomiting (CINV) in patients receiving moderately or highly emetogenic (MoHE) treatment: systematic review and meta-analysis. Support Care Cancer. 2011; 19(6): 823-832. DOI: 10.1007/s00520-010-0908-8.
250 Jordan K, Hinke A, Grothey A, et al. A meta-analysis comparing the efficacy of four 5-HT3-receptor antagonists for acute chemotherapy-induced emesis. Support Care Cancer. 2007; 15(9): 1023-1033.
251 Wu SJ, Xiong XZ, Lin YX, et al. Comparison of the efficacy on ondansetron and granisetron to prevent postoperative nausea and vomiting after laparoscopic cholecystectomy: a systematic review and meta-analysis. Surg Laparosc Endosc Percutan Tech. 2013; 23(1): 79-87. DOI: 10.1097/SLE.0b013e31827549e8.
252 Tang DH, Malone DC. A network meta-analysis on the efficacy of serotonin type 3 receptor antagonists used in adults during the first 24 hours for post-operative nausea and vomiting prophylaxis. Clin Ther. 2012; 34(2): 282-294. DOI: 10.1016/j.clinthera.2012.01.007.
253 Tricco AC, Soobiah, Blondal E, et al. Comparative safety of serotonin (5-HT3) receptor antagonists in patients undergoing surgery: a systematic review and network meta-analysis. BMC Med. 2015; 13: 136. DOI: 10.1186/s12916-015-0371-y.
254 Tricco AC, Soobiah C, Blondal E, et al. Comparative safety of serotonin (5-HT3) receptor antagonists in patients undergoing surgery: a systematic review and network meta-analysis. BMC Med. 2015; 13: 142. DOI. 10.1186/s12916-015-0379-3.
255 Wu SJ, Xiong Xz, Cheng TY, et al. Efficacy of ondansetron vs. metoclopramide in prophylaxis of postoperative nausea and vomiting after laparoscopic cholecystectomy: a systematic review and meta-analysis. Hepatogastroenterology. 2012; 59 (119): 2064-2074.
256 Carlisle JB, Stevenson CA. Drugs for preventing postoperative nausea and vomiting. Cochrane Database Syst Rev. 2006; 3:CD004125.